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(54) Title: METHODS AND COMPOSITIONS FOR DIAGNOSING DYSPLASIA

(57) Abstract: Methods and compositions are disclosed for detecting dysplasia in a tissue sample, screening candidate compounds for the ability to inhibit growth of a cancer cell, predicting predisposition to adenocarcinoma and treating cancer based on gene expression profiles.

METHODS AND COMPOSITIONS FOR DETECTING DYSPLASIA

TECHNICAL FIELD

The present invention relates to nucleic acid sequences, and compositions and uses therefore, which have been shown to be differentially expressed in high-grade dysplasia and which are useful as markers for the detection of high-grade dysplasia in a patient, and are implicated in the development of adenocarcinoma.

BACKGROUND OF THE INVENTION

The incidence of esophageal adenocarcinoma is rising in Western Countries, replacing squamous cell carcinoma as the most common neoplasm of the esophagus in white males and increasing in other ethnic groups (Devesa et al., Cancer 83:2049-2053 (1998); and Bollschweiler et al., Cancer 92:549-555 (2001)). Barrett's esophagus (BE) is the primary recognized risk factor for esophageal adenocarcinoma. BE results from repeated injury to the esophageal mucosa and develops in a subset of patients with chronic gastrointestinal reflux disease. It is characterized by a metaplastic change of squamous esophageal epithelium to intestinalized columnar mucosa (Csendes et al., Dis. Esoph 13:5-11 (2000); Cameron et al., New Eng. J. Med. 313:857-859 (1985); and Drewitz et al., Amer. J. Gastroenterol 92:212-215 (1997)).

Barrett's esophagus is found in 6% -16% of patients undergoing upper gastrointestinal endoscopy for gastroesophageal reflux, and it is estimated that a substantial patient population remains undiagnosed (Sarr et al., Amer. J. Surgery 149:187-193 (1985); Winters et al., Gastroenterology 92:118-124 (1985); Cameron et al., Gastroenterology 99:918-922 (1990); and Cameron et al., Gastroenterology 103:1241-1245 (1992)). The risk of developing esophageal carcinoma is 30 – 150 times greater in patients with BE. The outlook for patients diagnosed with adenocarcinoma is poor, with a 5 year survival rate of 10 – 15% (Streitz et al.,

Ann. Surg. 213:122-125 (1991); Menke-Pluymers et al., Gut 33:1454-1458 (1992); and Lerut et al., J. Thorac. Cariovasc. Surg. 107:1059-1066 (1994)). Patients with BE are placed on surveillance programs, although the absolute risk of developing adenocarcinoma in the context of BE remains relatively low, estimated at approximately 0.5% per patient year (Drewitz et al., Amer. J. Gastroenterol 92:212-215; O'Connor et al., Am. J. Gastroenterol 94:2037-2042 (1999); Spechler et al., JAMA 285:2331-2338 (2001); and Shaheen et al., Gastroenterology 119:333-338 (2000)). The value and cost-effectiveness of surveillance programs continue to be debated due to lack of understanding of the natural history of BE, the difficulty in obtaining representative biopsies by random sampling due to the heterogeneous nature of intestinal metaplasia, and inter-observer variability in endoscopic and histopathologic diagnosis (Falk, Gastroenterology 122:1569-1591 (2002); Sampliner, Am. J Gastroenterol. 93:1028-1032 (1998); and Alikhan et al., Gastrointest. Endosc. 50:23-26 (1999)). A metaplasia-dysplasia-carcinoma sequence has been described for BE and genetic changes involving cell cycle abnormalities, DNA ploidy, mutations, and amplification and expression of oncogenes have been identified (al-Kasspooles et al., Internat. J. Cancer 54:213-219 (1993); Vissers et al., Anticancer Res. 21:3813-3820 (2001); Bani-Hani et al., J. Natl. Cancer Inst. 92:1316-1321 (2000); Walch et al., Am. J. Pathol. 156:555-566 (2000); Wong et al., Cancer Res. 61:8284-8289 (2001); and Romagnoli et al., Laboratory Investigation 81:241-247 (2001)). There is a need for reliable detection of high-grade dysplasia and diagnosis of patients, such as BE patients, likely to develop adenocarcinoma, thereby allowing the disease to be monitored and treated early in its progression.

SUMMARY OF THE INVENTION

Generally, the present invention is based on the discovery that it is possible to detect high-grade dysplasia in a patient suspected of experiencing dysplasia, such as dysplasia associated with gastrointestinal reflux disease, such as Barrett's esophagus, or colon tissue dysplasia, by determining expression is an esophageal or colon biopsy from the patient wherein at least eight genes selected from a group of genes are expressed at a level of at least 1.5 fold over expression in a control sample. The control sample may comprise an esophageal or colon biopsy from a normal patient (i.e. one not experiencing gastrointestinal reflux disease) or from pooled samples of normal epithelial tissue (such as from normal liver, lung and kidney tissue). The group of high-grade dysplasia (HGD) gene markers, and their encoded polypeptides, comprise ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2);

AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44). HGD marker polypeptides refer to the polypeptides encoded by the HGD gene markers.

In an aspect, the invention involves a method for the diagnosis of esophageal high-grade dysplasia (HGD) in a patient, comprising establishing increased expression of at least eight genes (listed here with the polypeptide encoded by the gene) selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor,

NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44); and comparing expression of the genes to a baseline expression of the genes in normal tissue controls; wherein an increase of at least 1.5-fold in expression (and/or p value < 0/07) of the genes from the group relative to the baseline indicates that the patient is experiencing esophageal high-grade dysplasia. In an embodiment of the invention, the tissue is human tissue.

In another embodiment, the invention involves a method of identifying a patient susceptable to esophageal adenocarcoma, comprising diagnosing esophageal high-grade dysplasia in a patient by establishing increased expression of at least eight genes selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43); and comparing expression of the genes to a baseline expression of the genes in

normal tissue controls; wherein an increase of at least 1.5-fold in expression of the genes from the group relative to the baseline indicates that the patient is experiencing esophageal high-grade dysplasia. Alternatively, the patient may be susceptible to colon carcinoma and the diagnosing of high-grade dysplasia is by similarly determining expression of at least eight genes of the above group in a test colon tissue sample compared to a normal colon tissue sample.

In still another embodiment, the invention involves a method for determining whether an esophageal tissue is predisposed to a neo-plastic transformation, comprising determining whether in a cell from the esophageal tissue at least eight nucleic acid sequences selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43) is expressed at least 1.5-fold above baseline expression in a normal tissue control. In an embodiment, the tissue is human tissue.

In another aspect, the invention involves a method for the diagnosis of esophageal high-grade dysplasia in a patient, comprising establishing the level of expression a polypeptide encoded by at least eight genes selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog,

NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43); and comparing expression of the at least eight genes from the group to a baseline expression of the genes in normal tissue controls; wherein an increase of at least 1.5-fold in expression of the polypeptide encoded by the genes from the group relative to the baseline indicates that the patient has esophageal dysplasia.

In an embodiment, the method involves contacting a HGD cell or a cancer cell with an antibody that binds specifically to a polypeptide, or fragment thereof, encoded by a gene selected from the group of HGD marker genes or cancer marker genes as disclosed herein.

In an embodiment, the method involves determining expression of at least 8 of the genes of the group of HGD marker genes using by nucleic acid miroarray analysis. In further embodiment, the microarray comprises nucleic acid sequences of at least 20 nucleotides derived from at least eight of the genes from the following group: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase,

NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43).

In another embodiment, the invention involves analysis using a microarray comprising nucleic acid probe sequences comprising at least 20 contiguous nucleotides from at least 8 genes selected from the group of HGD marker genes: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43).

In a further embodiment, the methods of detecting high-grade dysplasia, diagnosing high-grade dysplasia, or prognosing development of cancer from detected high-grade dysplasia involves determining expression of at least eight genes from the group of HGD markers disclosed herein above as determined by an analysis method including, but not limited to polymerase chain reaction analysis, real-time polymerase chain reaction analysis, Taqman® polymerase chain reaction analysis, nucleic acid hybridization, fluorescent *in situ* hybridization and non-fluorescent *in situ* hybridization (e.g. radioactive, calorimetric, enzymatic or enzyme-linked detection methods for in situ hybridization). Where the method of the invention involves determining increased expression of polypeptides encoded by at least eight HGD marker genes as disclosed herein above, an embodiment of the method involves analysis using an antibody capable of specifically binding to a polypeptide, or a fragment thereof, encoded by a HGD marker gene.

In an alternative embodiment, the analytical methods of the invention involve probes or targets labelled with radionuclides or enzymatic labels such that expression of a gene or polypeptide is determinable.

In an embodiment of any of the methods or compositions of the invention, the dysplasia is high-grade dysplasia of esophagus tissue and the cancer is esophageal adenocarcinoma. Alternatively the patient is a human patient.

In another aspect, the invention involves a method of treating high-grade esophageal dysplasia or inhibiting or preventing cancer in a patient in need of such treatment, the method comprising administering to the patient a compound capable of decreasing expression of a gene selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ

ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43).

In still another aspect, the invention involves a method of treating high-grade esophageal dysplasia or inhibiting or preventing cancer in a patient in need of such treatment, the method comprising administering to the patient a compound capable of decreasing expression of a polypeptide encoded by a gene selected from the HGD marker genes.

In still another aspect, the invention involves a method of treating high-grade esophageal dysplasia or inhibiting or preventing cancer in a patient in need of such treatment, the method comprising administering to the patient a compound capable of inhibiting activity of a polypeptide encoded by a gene which is one of at least eight genes selected from the group of HGD marker genes as disclosed herein. In an embodiment, the compound is an antagonist of the polypeptide. In a further embodiment, the antagonist is an antibody, such as a monoclonal antibody or a humanized monoclonal antibody.

In a further aspect, the invention involves a method of screening for candidate drugs which inhibits or prevents progression from dysplasia to adenocarcinoma, the method comprising contacting a cell with a candidate drug, and assaying inhibition of progression from high-grade dysplasia to cancer in the cell, wherein the cell, prior to contacting with the candidate drug, expresses at least eight genes at a level at least 1.5-fold increased relative to a normal tissue baseline level, wherein the genes are selected from group of HGD marker genes as disclosed herein.

In another aspect, the invention involves a method of inhibiting or preventing progression from high-grade dysplasia to cancer in a patient by administering a drug identified by screening for candidate drugs which inhibits or prevents progression from dysplasia to adenocarcinoma, the method comprising contacting a cell with a candidate drug, and assaying

inhibition of progression from high-grade dysplasia to cancer in the cell, wherein the cell, prior to contacting with the candidate drug, expresses at least eight genes at a level at least 1.5-fold increased relative to a normal tissue baseline level, wherein the genes are selected from group of HGD marker genes as disclosed herein.

In another aspect, the invention involves a compound capable of inhibiting or preventing the progression from high-grade dysplasia to cancer in a patient. In an embodiment of the invention the compound is identified by screening for a candidate drug which inhibits or prevents progression from dysplasia to adenocarcinoma, the method comprising contacting a cell expressing at least 1.5-fold relative to a normal tissue baseline level at least eight genes selected from the group of HGD marker genes as disclosed herein, with a candidate drug, and assaying inhibition of progression from high-grade dysplasia to cancer in the cell. In an embodiment, the invention involves a pharmaceutical composition comprising a compound capable of inhibiting or preventing the progression from high-grade dysplasia to cancer in a patient, and a pharmaceutically acceptable carrier.

In still another aspect, the invention involves detecting cancer in a patient by determining that a gene, or the polypeptide it encodes, selected from the group consisting of CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:45 or 46), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:47 or 48), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:23 or 24), CFTR (chloride channel, NM_000492) (SEQ ID NO:49 or 50), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:51 or 52), PRSS8 (serine protease, NM_002773) (SEQ ID NO:7 or 8), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:27 or 28), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:3 or 4), EGFR (NM_005228) (SEQ ID NO:53 or 54), EPHB2 (NM_004442) (SEQ ID NO:55 or 56), CRIPTO CR-1 (NM_003212) (SEQ ID NO:57 or 58), Eprin B1 (NM_004429) (SEQ ID NO:59 or 60), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:61 or 62), MMP26 (NM_021801) (SEQ ID NO:63 or 64), ADAM10 (NM_001110) (SEQ ID NO:65 or 66), ADAM8 (NM_001109) (SEQ ID NO:5 or 6), ADAM1 (XM_132370) (SEQ ID NO:67 or 68), TIM1 (NM_003254) (SEQ ID NO:69 or 70), MUC1 (XM_053256) (SEQ ID NO:71 or 72), CEA (NM_004363) (SEQ ID NO:73 or 74), NCA (NM_002483) (SEQ ID NO:75 or 76), Follistatin (NM_006350) (SEQ ID NO:77 or 78), Claudin 1 (NM_021101) (SEQ ID NO:79 or 80), Claudin 14 (NM_012130) (SEQ ID NO:81 or 82), tenascin-R (NM_003285) (SEQ ID NO:83 or 84), CAD3 (NM_001793) (SEQ ID NO:85 or 86), AXO1 (NM_005076) (SEQ ID

NO:9 or 10), CONT (NM_001843) (SEQ ID NO:87 or 88), Osteopontin (NM_000582) (SEQ ID NO:89 or 90), Galectin 8 (NM_006499) (SEQ ID NO:91 or 92), PGS1 (bihlycan, NM_001711) (SEQ ID NO:93 or 94), Frizzled 2 (NM_001466) (SEQ ID NO:95 or 96), ISLR (NM_005545) (SEQ ID NO:97 or 98), FLJ23399 (NM_022763) (SEQ ID NO:99 or 100), TEM1 (NM_020404) (SEQ ID NO:101 or 102), Tie2 ligand2 (NM_001147) (SEQ ID NO:103 or 104), STC-2 (NM_003714) (SEQ ID NO:19 or 20), VEGFC (NM_005429) (SEQ ID NO:105 or 106), tPA (NM_000930) (SEQ ID NO:107 or 108), Endothelin 1 (NM_001955) (SEQ ID NO:1 or 2), Thrombomodulin (NM_000361) (SEQ ID NO:109 or 110), TF (NM_001993) (SEQ ID NO:111 or 112), GPR4 (NM_005282) (SEQ ID NO:113 or 114), GPR66 (NM_006056) (SEQ ID NO:115 or 116), SLC22A2 (NM_003058) ((SEQ ID NO:117 or 118), MLSN1 (NM_002420) (SEQ ID NO:119 or 120), and ATN2 (Na/K transport, NM_000702) (SEQ ID NO:121 or 122) is expressed at a level of about 1.5-fold in a test sample above the level of expression in a normal tissue sample of the same tissue type. The test sample is generally from a patient suspected of experiencing cancer, including, but not limited to, adenocarcinoma, esophageal adenocarcinoma, or colon cancer. The test sample is generally from the esophagus or colon of the patient. In an embodiment, at least two, alternatively at least three, alternatively at least five, and alternatively at least eight genes selected from the above group is upregulated in cancer tissue at 1.5-fold relative to normal tissue. Detection of the up-regulation of these genes is determined by, for example, hybridization analysis as standard in the and disclosed herein, as well as through antibody binding analysis of the level polypeptides expressed by the up-regulated gene or genes.

In an embodiment, the invention involves treatment by contacting a cancer cell with a compound that inhibits expression of at least one, optionally at least two, at least three, at least five, or at least eight genes, or the polypeptides encoded by the genes, selected from the group consisting of CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:45 or 46), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:47 or 48), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:23 or 24), CFTR (chloride channel, NM_000492) (SEQ ID NO:49 or 50), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:51 or 52), PRSS8 (serine protease, NM_002773) (SEQ ID NO:7 or 8), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:27 or 28), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:3 or 4), EGFR (NM_005228) (SEQ ID NO:53 or 54), EPHB2 (NM_004442) (SEQ ID NO:55 or 56), CRIPTO CR-1 (NM_003212) (SEQ ID NO:57 or 58), Eprin B1 (NM_004429) (SEQ ID NO:59 or 60), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:61 or 62), MMP26

(NM_021801) (SEQ ID NO:63 or 64), ADAM10 (NM_001110) (SEQ ID NO:65 or 66), ADAM8 (NM_001109) (SEQ ID NO:5 or 6), ADAM1 (XM_132370) (SEQ ID NO:67 or 68), TIM1 (NM_003254) (SEQ ID NO:69 or 70), MUC1 (XM_053256) (SEQ ID NO:71 or 72), CEA (NM_004363) (SEQ ID NO:73 or 74), NCA (NM_002483) (SEQ ID NO:75 or 76), Follistatin (NM_006350) (SEQ ID NO:77 or 78), Claudin 1 (NM_021101) (SEQ ID NO:79 or 80), Claudin 14 (NM_012130) (SEQ ID NO:81 or 82), tenascin-R (NM_003285) (SEQ ID NO:83 or 84), CAD3 (NM_001793) (SEQ ID NO:85 or 86), AXO1 (NM_005076) (SEQ ID NO:9 or 10), CONT (NM_001843) (SEQ ID NO:87 or 88), Osteopontin (NM_000582) (SEQ ID NO:89 or 90), Galectin 8 (NM_006499) (SEQ ID NO:91 or 92), PGS1 (bihlycan, NM_001711) (SEQ ID NO:93 or 94), Frizzled 2 (NM_001466) (SEQ ID NO:95 or 96), ISLR (NM_005545) (SEQ ID NO:97 or 98), FLJ23399 (NM_022763) (SEQ ID NO:99 or 100), TEM1 (NM_020404) (SEQ ID NO:101 or 102), Tie2 ligand2 (NM_001147) (SEQ ID NO:103 or 104), STC-2 (NM_003714) (SEQ ID NO:19 or 20), VEGFC (NM_005429) (SEQ ID NO:105 or 106), tPA (NM_000930) (SEQ ID NO:107 or 108), Endothelin 1 (NM_001955) (SEQ ID NO:1 or 2), Thrombomodulin (NM_000361) (SEQ ID NO:109 or 110), TF (NM_001993) (SEQ ID NO:111 or 112), GPR4 (NM_005282) (SEQ ID NO:113 or 114), GPR66 (NM_006056) (SEQ ID NO:115 or 116), SLC22A2 (NM_003058) ((SEQ ID NO:117 or 118), MLSN1 (NM_002420) (SEQ ID NO:119 or 120), and ATN2 (Na/K transport, NM_000702) (SEQ ID NO:121 or 122). In another embodiment, treatment is by contacting the cancer cell with a compound that inhibits the production or activity of a polypeptide of the above group and/or encoded by a gene of the above group. Where inhibition of a polypeptide is desired, the compound is often an antibody specific for the polypeptide, is often a monoclonal antibody such as a humanized antibody.

In yet another aspect, the invention involves a method of screening a candidate compound for the ability to inhibit cancer cell growth or cause cancer cell death by contacting the candidate compound with a cancer cell expressing a gene or polypeptide selected from the following group: CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:45 or 46), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:47 or 48), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:23 or 24), CFTR (chloride channel, NM_000492) (SEQ ID NO:49 or 50), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:51 or 52), PRSS8 (serine protease, NM_002773) (SEQ ID NO:7 or 8), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:27 or 28), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:3 or 4), EGFR (NM_005228) (SEQ ID NO:53 or 54), EPHB2 (NM_004442) (SEQ ID NO:55 or

56), CRIPTO CR-1 (NM_003212) (SEQ ID NO:57 or 58), Eprin B1 (NM_004429) (SEQ ID NO:59 or 60), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:61 or 62), MMP26 (NM_021801) (SEQ ID NO:63 or 64), ADAM10 (NM_001110) (SEQ ID NO:65 or 66), ADAM8 (NM_001109) (SEQ ID NO:5 or 6), ADAM1 (XM_132370) (SEQ ID NO:67 or 68), TIM1 (NM_003254) (SEQ ID NO:69 or 70), MUC1 (XM_053256) (SEQ ID NO:71 or 72), CEA (NM_004363) (SEQ ID NO:73 or 74), NCA (NM_002483) (SEQ ID NO:75 or 76), Follistatin (NM_006350) (SEQ ID NO:77 or 78), Claudin 1 (NM_021101) (SEQ ID NO:79 or 80), Claudin 14 (NM_012130) (SEQ ID NO:81 or 82), tenascin-R (NM_003285) (SEQ ID NO:83 or 84), CAD3 (NM_001793) (SEQ ID NO:85 or 86), AXO1 (NM_005076) (SEQ ID NO:9 or 10), CONT (NM_001843) (SEQ ID NO:87 or 88), Osteopontin (NM_000582) (SEQ ID NO:89 or 90), Galectin 8 (NM_006499) (SEQ ID NO:91 or 92), PGS1 (bihlycan, NM_001711) (SEQ ID NO:93 or 94), Frizzled 2 (NM_001466) (SEQ ID NO:95 or 96), ISLR (NM_005545) (SEQ ID NO:97 or 98), FLJ23399 (NM_022763) (SEQ ID NO:99 or 100), TEM1 (NM_020404) (SEQ ID NO:101 or 102), Tie2 ligand2 (NM_001147) (SEQ ID NO:103 or 104), STC-2 (NM_003714) (SEQ ID NO:19 or 20), VEGFC (NM_005429) (SEQ ID NO:105 or 106), tPA (NM_000930) (SEQ ID NO:107 or 108), Endothelin 1 (NM_001955) (SEQ ID NO:1 or 2), Thrombomodulin (NM_000361) (SEQ ID NO:109 or 110), TF (NM_001993) (SEQ ID NO:111 or 112), GPR4 (NM_005282) (SEQ ID NO:113 or 114), GPR66 (NM_006056) (SEQ ID NO:115 or 116), SLC22A2 (NM_003058) ((SEQ ID NO:117 or 118), MLSN1 (NM_002420) (SEQ ID NO:119 or 120), and ATN2 (Na/K transport, NM_000702) (SEQ ID NO:121 or 122), wherein gene expression of at least one, at least two, at least three, at least five, or at least eight genes selected from the group are expressed at a level at least about 1.5-fold above the level in normal control tissue. Where the candidate compound is an antibody, the antibody is alternatively a polyclonal, monoclonal, humanized antibody, a Fab, a F(ab')2, or a binding fragment of any one of these compounds.

In an embodiment, the sequences which are used to determine sequence identity or similarity are selected from the sequences described herein. Optionally, sequence variants are naturally occurring allelic variants, sequence variants or splice variants of these sequences. Sequence identity is typically calculated using the BLAST algorithm, described in Altschul et al Nucleic Acids Res. 25,3389-3402 (1997) with the BLOSUM62 default matrix.

In one embodiment, nucleic acid homology can be determined through hybridisation studies. Nucleic acids which hybridise under stringent conditions to the nucleic acids of the

invention are considered high-grade esophageal dysplasia sequences. Under stringent conditions, hybridisation will most preferably occur at 42°C in 750 mM NaCl, 75 mM trisodium citrate, 2% SDS, 50% formamide, 1X Denhart's, 10% (w/v) dextran sulphate and 100 pg/ml denatured salmon sperm DNA. Useful variations on these conditions will be readily apparent to those skilled in the art. The washing steps which follow hybridization most preferably occur at 65°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

As a result of the degeneracy of the genetic code, a number of polynucleotide sequences encoding polypeptides of the invention, some that may have minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention includes each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring high-grade esophageal dysplasia sequences, and all such variations are to be considered as being specifically disclosed.

The polynucleotides of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified, or may contain non-natural or derivatised nucleotide bases as will be appreciated by those skilled in the art. Such modifications include labels, methylation, intercalators, alkylators and modified linkages. In some instances it may be advantageous to produce nucleotide sequences encoding high-grade esophageal dysplasia sequences of the invention, or their derivatives, possessing a substantially different codon usage than that of the naturally occurring gene. For example, codons may be selected to increase the rate of expression of the peptide in a particular prokaryotic or eukaryotic host corresponding with the frequency that particular codons are utilized by the host. Other reasons to alter the nucleotide sequence encoding high-grade esophageal dysplasia sequences of the invention, or their derivatives, without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

In some instances, useful nucleic acid sequences up-regulated in high-grade esophageal dysplasia of the invention are fragments of larger genes and may be used to identify and obtain

corresponding full- length genes. Full-length sequences of the genes selected from the HGD gene marker group or cancer gene marker group of the invention can be obtained using a partial gene sequence using methods known per se to those skilled in the art. For example,"restriction-site PCR" may be used to retrieve unknown sequence adjacent to a portion of DNA whose sequence is known. In this technique universal primers are used to retrieve unknown sequence. Inverse PCR may also be used, in which primers based on the known sequence are designed to amplify adjacent unknown sequences. These upstream sequences may include promoters and regulatory elements. In addition, various other PCR-based techniques may be used, for example a kit available from Clontech (Palo Alto, California) allows for a walking PCR technique, the 5'RACE kit (Gibco-BRL) allows isolation of additional sequence while additional 3'sequence can be obtained using practised techniques.

The present invention allows for the preparation of purified high-grade dysplasia polypeptide (i.e. a polypeptide encoded by a gene disclosed herein as up-regulated in high-grade esophageal dysplasia) or protein, from the polynucleotides of the present invention or variants thereof. In order to do this, host cells may be transfected with a nucleic acid molecule as described above. Typically said host cells are transfected with an expression vector comprising a nucleic acid encoding a high-grade esophageal dysplasia protein according to the invention. Cells are cultured under the appropriate conditions to induce or cause expression of the high-grade esophageal dysplasia protein. The conditions appropriate for high-grade esophageal dysplasia protein expression will vary with the choice of the expression vector and the host cell, and will be easily ascertained by one skilled in the art.

A variety of expression vector/host systems may be utilized to contain and express the high-grade dysplasia sequences of the invention and are well known in the art. These include, but are not limited to, microorganisms such as bacteria transformed with plasmid or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e. g., baculovirus); or mouse or other animal or human tissue cell systems. In a preferred embodiment the high-grade esophageal dysplasia proteins of the invention are expressed in mammalian cells using various expression vectors including plasmid, cosmid and viral systems such as adenoviral, retroviral or vaccinia virus expression systems. The invention is not limited by the host cell employed.

The polynucleotide sequences, or variants thereof, of the present invention can be stably expressed in cell lines to allow long term production of recombinant proteins in mammalian systems. These sequences can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. The selectable marker confers resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode a protein of the invention may be designed to contain signal sequences which direct secretion of the protein through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, glycosylation, phosphorylation, and acylation. Post-translational cleavage of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells having specific cellular machinery and characteristic mechanisms for post- translational activities (e. g., CHO or HeLa cells), are available from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the foreign protein.

When large quantities of protein are needed such as for antibody production, vectors which direct high levels of high-grade esophageal dysplasia gene expression may be used such as those containing the T5 or T7 inducible bacteriophage promoter.

The present invention also includes the use of the expression systems described above in generating and isolating fusion proteins which contain important functional domains of the protein. These fusion proteins are used for binding, structural and functional studies as well as for the generation of appropriate antibodies.

In order to express and purify the protein as a fusion protein, the appropriate cDNA sequence is inserted into a vector which contains a nucleotide sequence encoding another peptide (for example, glutathionine succinyl transferase). The fusion protein is expressed and recovered from prokaryotic or eukaryotic cells. The fusion protein can then be purified by affinity chromatography based upon the fusion vector sequence. The relevant protein can subsequently be obtained by enzymatic cleavage of the fusion protein.

In one embodiment, a fusion protein may be generated by the fusion of a high-grade dysplasia polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino-or carboxy-terminus of the high-grade esophageal dysplasia polypeptide. The presence of such epitope-tagged forms of a high-grade esophageal dysplasia polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the high-grade dysplasia polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag.

Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine or poly-histidine-glycine tags and the c- myc tag and antibodies thereto. Fragments of high-grade dysplasia polypeptide may also be produced by direct peptide synthesis using solid-phase techniques. Automated synthesis may be achieved by using the ABI 433A Peptide Synthesizer (Applied Biosystems, Foster City, CA). Various fragments of high-grade dysplasia polypeptide may be synthesized separately and then combined to produce the full-length molecule.

In a further aspect of the invention there is provided a method of preparing a polypeptide as described above, comprising the steps of: (1) culturing the host cells under conditions effective for production of the polypeptide; and (2) harvesting the polypeptide.

Substantially purified high-grade dysplasia polypeptide or fragments thereof can then be used in further biochemical analyses to establish secondary and tertiary structure for example by x-ray crystallography of the protein or by nuclear magnetic resonance (NMR). Determination of structure allows for the rational design of pharmaceuticals to interact with the protein, alter protein charge configuration or charge interaction with other proteins, or to alter its function in the cell.

With the identification of the high-grade esophageal dysplasia marker gene nucleotide sequences and the polypeptide sequences encoded by them, probes and antibodies raised to the genes can be used in a variety of hybridisation and immunological assays to screen for and detect the presence of either a normal or mutated gene or gene product.

In addition the nucleotide and protein sequences of the high-grade dysplasia genes provided in this invention enable therapeutic methods for the treatment of cancer, such as adenocarcinoma associated with one or more of these genes, enable screening of compounds for therapeutic intervention, and also enable methods for the diagnosis or prognosis of cancer associated with the these genes. Examples of such cancers include, but are not limited to, esophageal adenocarcinoma.

Transducing retroviral vectors are often used for producing a cell line expressing a gene above the level of expression in a cell lacking the additional copy of the gene. Such a cell is useful according to the invention for the production of a cell line useful for screening candidate compounds capable of reducing expression of a gene associated with high-grade esophageal dysplasia, reducing expression of a polypeptide encoded by the gene, or inhibiting activity of the polypeptide, such that the cell does not progress from dysplasia to cancer. The full-length high-grade dysplasia gene, or portions thereof, can be cloned into a retroviral vector and expression can be driven from its endogenous promoter or from the retroviral long terminal repeat or from a promoter specific for the target cell type of interest. Other viral vectors can be used and include, as is known in the art, adenoviruses, adeno-associated virus, vaccinia virus, papovaviruses, lentiviruses and retroviruses of avian, murine and human origin.

The viral vector described herein above is also useful for gene therapy to reduce the activity of the high-grade dysplasia genes of the invention, such as by antisense expression inhibition or RNA interference (see, for example, Paddison, P.J. et al., Genes & Development 16:948-958 (2002) and Brummelkamp, T.R. et al., Science 296:550-553 (2002)). Gene therapy would be carried out according to established methods (Friedman, 1991; Culver, 1996). A vector containing a copy of a high-grade esophageal dysplasia gene linked to expression control elements and capable of replicating inside the cells is prepared. Alternatively the vector may be replication deficient and may require helper cells or helper virus for replication and virus production and use in gene therapy.

Gene transfer using non-viral methods of infection can also be used. These methods include direct injection of DNA, uptake of naked DNA in the presence of calcium phosphate, electroporation, protoplast fusion or liposome delivery. Gene transfer can also be achieved by delivery as a part of a human artificial chromosome or receptor- mediated gene transfer. This involves linking the DNA to a targeting molecule that will bind to specific cell- surface receptors to induce endocytosis and transfer of the DNA into mammalian cells. One such technique uses poly-L-lysine to link asialoglycoprotein to DNA. An adenovirus is also added to the complex to disrupt the lysosomes and thus allow the DNA to avoid degradation and move to the nucleus. Infusion of these particles intravenously has resulted in gene transfer into hepatocytes.

Inhibiting high-grade esophageal dysplasia gene or polypeptide function that are up-regulated in cancer can be achieved in a variety of ways as would be appreciated by those skilled in the art. Typically, a vector expressing the complement of a polynucleotide encoding a high-grade dysplasia gene of the invention may be administered to a subject to treat or prevent a disorder associated with increased activity and/or expression of the gene including, but not limited to, those described above.

Antisense strategies may use a variety of approaches including the use of antisense oligonucleotides, ribozymes, DNAzymes, injection of antisense RNA and transfection of antisense RNA expression vectors. Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art (see, for example, Goldman, CK. et al., Nature Biotechnology 15: 462-466 (1997))

Where purified protein or polypeptide is used to produce antibodies which specifically bind a high-grade dysplasia protein, the antibody(ies) are used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues that express the protein. Such antibodies may include, but are not limited to,

polyclonal, monoclonal, chimeric and single chain antibodies as would be understood by the person skilled in the art.

For the production of antibodies, various hosts including rabbits, rats, goats, mice, humans, and others may be immunized by injection with a protein of the invention or with any fragment or oligopeptide thereof, which has immunogenic properties. Various adjuvants may be used to increase immunological response and include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface-active substances such as lysolecithin. Adjuvants used in humans include BCG (bacilli Calmette-Guerin) and Corynebacterium parvum.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to the high-grade dysplasia of the invention have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of amino acids from these proteins may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to high-grade dysplasia polypeptides or proteins of the invention may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (For example, see Kohler, G. and Milstein, C., Nature 256:495-497 (1975); Kozbor, D. et al., Immunol. Methods 81:31-42 (1985); and Cole, S.P. et al., Mol. Cell Biol. 62:109-120 (1984)).

Antibodies may also be produced by inducing *in vivo* production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature.

Antibody fragments which contain specific binding sites for the high-grade esophageal dysplasia proteins may also be generated. For example, such fragments include fragments

produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(AB)2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (For example, see Huse, W. D. et al., Science 246:1275-1281 (1989)). Various immunoassays well known in art may be used for screening to identify antibodies having the desired specificity.

Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between a protein and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes is preferred, but a competitive binding assay may also be employed.

Candidate pharmaceutical agents or compounds encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having molecular weight of more than 100 and less than about 2,500 daltons. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids and steroids and peptides.

Agent screening techniques include, but are not limited to, utilising eukaryotic or prokaryotic host cells that are stably transformed with recombinant molecules expressing a particular high-grade dysplasia polypeptide of the invention, or fragment thereof, preferably in competitive binding assays. Binding assays will measure for the formation of complexes between the high-grade esophageal dysplasia polypeptide, or fragments thereof, and the agent being tested, or will measure the degree to which an agent being tested will interfere with the formation of a complex between the high-grade esophageal dysplasia polypeptide, or fragment thereof, and a known ligand.

Another technique for drug screening provides high- throughput screening for compounds having suitable binding affinity to a high-grade dysplasia polypeptide. In such a technique, large numbers of small peptide test compounds are synthesised on a solid substrate and can be assayed through high-grade esophageal dysplasia polypeptide binding and washing. Bound high-grade dysplasia polypeptide is then detected by methods well known in

the art. In a variation of this technique, purified polypeptides can be coated directly onto plates to identify interacting test compounds.

An additional method for drug screening involves the use of host eukaryotic cell lines which carry mutations in a particular high-grade dysplasia gene. The host cell lines are also defective at the polypeptide level. Other cell lines may be used where the gene expression of the high-grade esophageal dysplasia gene can be switched off or up-regulated. The host cell lines or cells are grown in the presence of various drug compounds and the rate of growth of the host cells is measured to determine if the compound is capable of regulating the growth of defective cells.

A high-grade esophageal dysplasia polypeptide encoded by an HGD marker gene may also be used for screening compounds developed as a result of combinatorial library technology. This provides a way to test a large number of different substances for their ability to modulate activity of a polypeptide. The use of peptide libraries is preferred with such libraries and their use known in the art.

A substance identified as a modulator of polypeptide function may be peptide or non-peptide in nature. Non-peptide "small molecules" are often preferred for many *in vivo* pharmaceutical applications. In addition, a mimic or mimetic of the substance may be designed for pharmaceutical use. The design of mimetics based on a known pharmaceutically active compound (i.e., a "lead compound") is a common approach to the development of novel pharmaceuticals. This is often desirable where the original active compound is difficult or expensive to synthesise or where it provides an unsuitable method of administration. In the design of a mimetic, particular parts of the original active compound that are important in determining the target property are identified. These parts or residues constituting the active region of the compound are known as its pharmacophore. Once found, the pharmacophore structure is modelled according to its physical properties using data from a range of sources including x-ray diffraction data and NMR. A template molecule is then selected onto which chemical groups which mimic the pharmacophore can be added. The selection can be made such that the mimetic is easy to synthesise, is likely to be pharmacologically acceptable, does not degrade in vivo and retains the biological activity of the lead compound. Further optimisation or modification can be carried out to select one or more final mimetics useful for *in vivo* or clinical testing.

It is also possible to isolate a target-specific antibody and then solve its crystal structure. In principle, this approach yields a pharmacophore upon which subsequent drug design can be based as described above. It may be possible to avoid protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody.

As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analogue of the original binding site. The anti-id could then be used to isolate peptides from chemically or biologically produced peptide banks.

In further embodiments, any of the genes, proteins, antagonists, antibodies, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents.

Selection of the appropriate agents may be made by those skilled in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, therapeutic efficacy with lower dosages of each agent may be possible, thus reducing the potential for adverse side effects.

In a further aspect a pharmaceutical composition and a pharmaceutically acceptable carrier may be administered to a patient diagnosed as experiencing high-grade esophageal dysplasia for the inhibition or prevention of progression of the disease to adenocarcinoma.

The pharmaceutical composition may comprise any one or more of a polypeptide as described above, typically a substantially purified high-grade esophageal dysplasia polypeptide, an antibody to a high-grade esophageal dysplasia polypeptide, a vector capable of expressing a high-grade esophageal dysplasia polypeptide, a compound which increases or decreases expression of a high-grade esophageal dysplasia gene, a candidate drug that restores wild-type activity to a high-grade esophageal dysplasia gene or an antagonist of a high-grade esophageal dysplasia gene.

The pharmaceutical composition may be administered to a subject to treat or prevent a cancer associated with decreased activity and/or expression of a high-grade esophageal dysplasia gene including, but not limited to, those provided above.

Pharmaceutical compositions in accordance with the present invention are prepared by mixing a polypeptide of the invention, or active fragments or variants thereof, having the desired degree of purity, with acceptable carriers, excipients, or stabilizers which are well known.

Acceptable carriers, excipients or stabilizers are nontoxic at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including absorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitrol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as Tween, Pluronics or polyethylene glycol (PEG).

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

Polynucleotide sequences encoding the high-grade esophageal dysplasia genes of the invention may be used for the diagnosis or prognosis of cancers associated with their dysfunction, or a predisposition to such cancers. Examples of such cancers include, but are not limited to, adenocarcinoma, such as in patients having Barrett's esophagus. Diagnosis or prognosis may be used to determine the severity, type or stage of the disease state in order to initiate an appropriate therapeutic intervention.

In another embodiment of the invention, the polynucleotides that may be used for diagnostic or prognostic purposes include oligonucleotide sequences, genomic DNA and complementary RNA and DNA molecules. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which mutations or abnormal expression of the relevant high-grade esophageal dysplasia gene may be correlated with disease. Genomic

DNA used for the diagnosis or prognosis may be obtained from body cells, such as those present in the blood, tissue biopsy, surgical specimen, or autopsy material. The DNA may be isolated and used directly for detection of a specific sequence or may be amplified by the polymerase chain reaction (PCR) prior to analysis. Similarly, RNA or cDNA may also be used, with or without PCR amplification. To detect a specific nucleic acid sequence, direct nucleotide sequencing, reverse transcriptase PCR (RT-PCR), hybridization using specific oligonucleotides, restriction enzyme digest and mapping, PCR mapping, RNAse protection, and various other methods may be employed.

Oligonucleotides specific to particular sequences can be chemically synthesized and labelled radioactively or non- radioactively and hybridised to individual samples immobilized on membranes or other solid-supports or in solution. The presence, absence or excess expression of a particular high-grade esophageal dysplasia gene may then be visualized using methods such as autoradiography, fluorometry, or colorimetry.

In a particular aspect, the nucleotide sequences encoding a high-grade esophageal dysplasia gene of the invention may be useful in assays that detect the presence of associated disorders, particularly those mentioned previously. The nucleotide sequences encoding the relevant high-grade esophageal dysplasia gene may be labelled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes.

After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding the high-grade esophageal dysplasia gene in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis or prognosis of a disorder associated with a mutation in a particular high-grade esophageal dysplasia gene of the invention, the nucleotide sequence of the relevant gene can be compared between normal tissue and diseased tissue in order to establish whether the patient expresses a mutant gene.

In order to provide a basis for the diagnosis or prognosis of a disorder associated with abnormal expression of a particular high-grade esophageal dysplasia gene of the invention, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding the relevant high-grade esophageal dysplasia gene, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used.

Another method to identify a normal or standard profile for expression of a particular high-grade esophageal dysplasia gene is through quantitative RT-PCR studies. RNA isolated from body cells of a normal individual, particularly RNA isolated from tumour cells, is reverse transcribed and real-time PCR using oligonucleotides specific for the relevant high-grade esophageal dysplasia gene is conducted to establish a normal level of expression of the gene.

Standard values obtained in both these examples may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays or quantitative RT-PCR studies may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding a particular high-grade esophageal dysplasia gene, or closely related molecules, may be used to identify nucleic acid sequences which encode the gene. The specificity of the probe, whether it is made from a highly specific region, e. g., the 5'regulatory region, or from a less specific region, *e.g.*, a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding the high-grade esophageal dysplasia gene, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the high-grade esophageal dysplasia encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of HGD marker genes disclosed in Table 4 or from genomic sequences including promoters, enhancers, and introns of the genes.

Means for producing specific hybridization probes for DNAs encoding the high-grade esophageal dysplasia genes of the invention include the cloning of polynucleotide sequences encoding these genes or their derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, and are commercially available. Hybridization probes may be labelled by radionuclides such as 32p or 35S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, or other methods known in the art.

According to a further aspect of the invention there is provided the use of a polypeptide as described above in the diagnosis or prognosis of a cancer associated with a high-grade esophageal dysplasia gene of the invention, or a predisposition to such cancers.

When a diagnostic or prognostic assay is to be based upon a high-grade esophageal dysplasia protein, a variety of approaches are possible. For example, diagnosis or prognosis can be achieved by monitoring differences in the electrophoretic mobility of normal and mutant proteins. Such an approach will be particularly useful in identifying mutants in which charge substitutions are present, or in which insertions, deletions or substitutions have resulted in a significant change in the electrophoretic migration of the resultant protein. Alternatively, diagnosis may be based upon differences in the proteolytic cleavage patterns of normal and mutant proteins, differences in molar ratios of the various amino acid residues, or by functional assays demonstrating altered function of the gene products.

In another aspect, antibodies that specifically bind a high-grade esophageal dysplasia gene of the invention may be used for the diagnosis or prognosis of cancers characterized by abnormal expression of the gene, or in assays to monitor patients being treated with the gene or agonists, antagonists, or inhibitors of the gene. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic or

prognostic assays include methods that utilize the antibody and a label to detect a high-grade esophageal dysplasia gene of the invention in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labelled by covalent or non- covalent attachment of a reporter molecule.

A variety of protocols for measuring a high-grade esophageal dysplasia gene of the invention, including ELISA, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of their expression. Normal or standard values for their expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to the high-grade esophageal dysplasia protein under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of any of the high-grade esophageal dysplasia genes expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

Once an individual has been diagnosed with a cancer, effective treatments can be initiated. These may include administering a selective agonist to the relevant mutant high-grade esophageal dysplasia gene so as to restore its function to a normal level or introduction of the wild-type gene, particularly through gene therapy approaches as described above. Typically, a vector capable of expressing the appropriate full-length high-grade esophageal dysplasia gene or a fragment or derivative thereof may be administered. In an alternative approach to therapy, a substantially purified high-grade esophageal dysplasia polypeptide and a pharmaceutically acceptable carrier may be administered, as described above, or drugs which can replace the function of or mimic the action of the relevant high-grade esophageal dysplasia gene may be administered.

In the treatment of cancers associated with increased high-grade esophageal dysplasia gene expression and/or activity, the affected individual may be treated with a selective antagonist such as an antibody to the relevant protein or an antisense (complement) probe to the corresponding gene as described above, or through the use of drugs which may block the action of the relevant high-grade esophageal dysplasia gene.

In further embodiments, complete cDNAs, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to detect or prognose a disorder, and to develop and monitor the activities of therapeutic agents. Microarrays may be prepared, used, and analyzed using methods known in the art (for example, see Schena, M. et al. PNAS USA 93:10614-10619 (1996); Heller, R.A. et al., PNAS USA 94:2150-2155 (1997); and Heller, M.J., Annual Review of Biomedical Engineering 4:129-53 (2002)).

The present invention also provides for the production of genetically modified (knock-out, knock-down, knock-in and transgenic), non-human animal models transformed with the DNA molecules of the invention. These animals are useful for the study of high-grade esophageal dysplasia gene function, to study the mechanisms of cancer as related to the high-grade esophageal dysplasia genes, for the screening of candidate pharmaceutical compounds, for the creation of explanted mammalian cell cultures which express the protein or mutant protein and for the evaluation of potential therapeutic interventions.

One of the high-grade esophageal dysplasia genes of the invention may have been inactivated by knock-out deletion, and knock-out genetically modified non-human animals are therefore provided.

Animal species which are suitable for use in the animal models of the present invention include, but are not limited to, rats, mice, hamsters, guinea pigs, rabbits, dogs, cats, goats, sheep, pigs, and non-human primates such as monkeys and chimpanzees. For initial studies, genetically modified mice and rats are highly desirable due to their relative ease of maintenance and shorter life spans. For certain studies, transgenic yeast or invertebrates may be suitable and preferred because they allow for rapid screening and provide for much easier handling. For longer term studies, non-human primates may be desired due to their similarity with humans.

To create an animal model for a mutated high-grade esophageal dysplasia gene of the invention several methods can be employed. These include generation of a specific mutation

in a homologous animal gene, insertion of a wild type human gene and/or a humanized animal gene by homologous recombination, insertion of a mutant (single or multiple) human gene as genomic or minigene cDNA constructs using wild type or mutant or artificial promoter elements or insertion of artificially modified fragments of the endogenous gene by homologous recombination. The modifications include insertion of mutant stop codons, the deletion of DNA sequences, or the inclusion of recombination elements (lox p sites) recognized by enzymes such as Cre recombinase.

To create a transgenic mouse, which is preferred, a mutant version of a particular high-grade esophageal dysplasia gene of the invention can be inserted into a mouse germ line using standard techniques of oocyte microinjection or transfection or microinjection into embryonic stem cells. Alternatively, if it is desired to inactivate or replace the endogenous high-grade esophageal dysplasia gene, homologous recombination using embryonic stem cells may be applied. For oocyte injection, one or more copies of the mutant or wild type high-grade esophageal dysplasia gene can be inserted into the pronucleus of a just-fertilized mouse oocyte. This oocyte is then reimplanted into a pseudo-pregnant foster mother. The liveborn mice can then be screened for integrants using analysis of tail DNA for the presence of human high-grade esophageal dysplasia gene sequences. The transgene can be either a complete genomic sequence injected as a YAC, BAC, PAC or other chromosome DNA fragment, a cDNA with either the natural promoter or a heterologous promoter, or a minigene containing all of the coding region and other elements found to be necessary for optimum expression. The genetically modified non-human animals as described above are useful for the screening of candidate pharmaceutical compounds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are graphs showing a distribution of expression of IL-1H1 (Fig. 1A) and CYP2J2 (Fig. 1B) in the dysplasia-carcinoma sequence in BE. Expression in normal epithelium and in esophageal epithelia from samples of Barrett's esophagus (BE), dysplasia (D), BE adjacent to andenocarcinoma (BE-CA); and adenocarcinoma (CA) are plotted. The vertical line denotes the average Z score in each disease group. Normal refers to the normal esophagus group. Dysplasia includes low- and high-grade dysplasia samples.

Figures 2A and 2B are graphs showing a distribution of expression of AGR2 (Fig. 2A) and NROB2 (Fig. 2B) in the dysplasia-carcinoma sequence in BE. Expression in esophageal epithelia from samples of Barrett's esophagus (BE), dysplasia (D), BE adjacent to andenocarcinoma (BE-CA); and adenocarcinoma (CA) are plotted. The vertical line denotes the average Z score in each disease group. Normal refers to pooled epithelia samples. Dysplasia includes low- and high-grade dysplasia samples.

Figures 3A and 3B are graphs showing a distribution of expression of TCF4 (Fig. 3A) and FLJ23399 (Fig. 3B) in the dysplasia-carcinoma sequence in BE. Expression in esophageal epithelia from samples of Barrett's esophagus (BE), dysplasia (D), BE adjacent to andenocarcinoma (BE-CA); and adenocarcinoma (CA) are plotted. The vertical line denotes the average Z score in each disease group. Normal refers to pooled epithelia samples. Dysplasia includes low- and high-grade dysplasia samples.

Figures 4A and 4B show the nucleic acid sequence (SEQ ID NO:1) and the amino acid sequence (SEQ ID NO:2) of ET-1 (endothelin-1, NM_001955).

Figures 5A and 5B show the nucleic acid sequence (SEQ ID NO:3) and the amino acid sequence (SEQ ID NO:4) of AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408).

Figures 6A and 6B show the nucleic acid sequence (SEQ ID NO:5) and the amino acid sequence (SEQ ID NO:6) of ADAM8 (NM_001109).

Figures 7A and 7B show the nucleic acid sequence (SEQ ID NO:7) and the amino acid sequence (SEQ ID NO:8) of PSS8 (Prostasin precursor, serine protease, NM_002773).

Figures 8A-8C show the nucleic acid sequence (SEQ ID NO:9) and Figure 8D shows the amino acid sequence (SEQ ID NO:10) of AXO1 (Axonin-1 precursor, NM_005076).

Figures 9A and 9B show the nucleic acid sequence (SEQ ID NO:11) and the amino acid sequence (SEQ ID NO:12) of NROB2 (Nuclear hormone receptor, NM_021969).

Figures 10A and 10B show the nucleic acid sequence (SEQ ID NO:13) and the amino acid sequence (SEQ ID NO:14) of TM7SF1 (NM_003272).

Figures 11A and 11B show the nucleic acid sequence (SEQ ID NO:15) and the amino acid sequence (SEQ ID NO:16) of DLDH (dihydrolipamide dehydrogenase, NM_000108).

Figures 12A and 12B show the nucleic acid sequence (SEQ ID NO:17) and the amino acid sequence (SEQ ID NO:18) of MAT2B (methionine adenosyltransferase II, beta, NM_013283).

Figures 13A and 13B show the nucleic acid sequence (SEQ ID NO:19) and the amino acid sequence (SEQ ID NO:20) of STC-2 (stanniocalcin-2, NM_003714).

Figures 14A and 14B show the nucleic acid sequence (SEQ ID NO:21) and the amino acid sequence (SEQ ID NO:22) of PPBI (alkaline phosphatase, intestinal precursor, NM_001631).

Figures 15A and 15B show the nucleic acid sequence (SEQ ID NO:23) and the amino acid sequence (SEQ ID NO:24) of SLNAC1 (sodium channel receptor SLNAC1, NM_004769).

Figures 16A and 16B show the nucleic acid sequence (SEQ ID NO:25) and the amino acid sequence (SEQ ID NO:26) of CAH4 (carbonic anhydrase iv precursor, NM_000717).

Figures 17A and 17B show shows the nucleic acid sequence (SEQ ID NO:27) and the amino acid sequence (SEQ ID NO:28) of PA21 (phopholipase a2 precursor, NM_000928).

Figures 18A and 18B show the nucleic acid sequence (SEQ ID NO: 29) and the amino acid sequence (SEQ ID NO:30) of PAR2 (proteinase activated receptor 2 precursor, NM_005242).

Figures 19A and 19B show the nucleic acid sequence (SEQ ID NO:31) and the amin acid sequence (SEQ ID NO:32) of IDE (insulin-degrading enzyme, NM_004969).

Figures 20A-20B show the nucleic acid sequence (SEQ ID NO:33) and Figure 20C shows the amino acid sequence (SEQ ID NO:34) of MYO1A (myosin-1A, NM_005379).

Figures 21A and 21B the nucleic acid sequence (SEQ ID NO:35) and the amin acid sequence (SEQ ID NO:36) of CYP2J2 (cytochrome P450 monooxygenase, NM_000775).

Figures 22A and 22B show the nucleic acid sequence (SEQ ID NO:37) and the amin acid sequence (SEQ ID NO:38) of PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214).

Figures 23A and 23B show the nucleic acid sequence (SEQ ID NO:39) and the amin acid sequence (SEQ ID NO:40) of CYB5 (cytochrome b5, 3' end, NM_001914).

Figures 24A and 24B show the nucleic acid sequence (SEQ ID NO:41) and the amin acid sequence (SEQ ID NO:42) of COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863).

Figures 25A and 25B show the nucleic acid sequence (SEQ ID NO:43) and the amin acid sequence (SEQ ID NO:44) of TCF4 (NM_030756).

Figures 26A-26B show the nucleic acid sequence (SEQ ID NO:45) and Figure 26C shows the amino acid sequence (SEQ ID NO:46) of CAD17 (liver-intestine cadherin, NM_004063).

Figures 27A and 27B show the nucleic acid sequence (SEQ ID NO:47) and the amino acid sequence (SEQ ID NO:48) of CLDN15 (claudin 15, NM_014343).

Figures 28A-28B show the nucleic acid sequence (SEQ ID NO:49) and Figure 28C shows the amino acid sequence (SEQ ID NO:50) of CFTR (chloride channel, NM_000492).

Figures 29A and 29B show the nucleic acid sequence (SEQ ID NO:51) and the amino acid sequence (SEQ ID NO:52) of H2R (histamine H2 receptor, NM_022304).

Figures 30A-30B show the nucleic acid sequence (SEQ ID NO:53) and Figure 30C shows the amino acid sequence (SEQ ID NO:54) of EGFR (epidermal growth factor receptor, NM_005228).

Figures 31A-31B show the nucleic acid sequence (SEQ ID NO:55) and Figure 31C shows the amino acid sequence (SEQ ID NO:56) of EPHB2, NM_004442).

Figures 32A and 32B show the nucleic acid sequence (SEQ ID NO:57) and the amino acid sequence (SEQ ID NO:58) of CRIPTO CR-1 (NM_003212).

Figures 33A and 33B show the nucleic acid sequence (SEQ ID NO:59) and the amino acid sequence (SEQ ID NO:60) of Eprin B1 (NM_004429).

Figures 34A and 34B show the nucleic acid sequence (SEQ ID NO:61) and the amino acid sequence (SEQ ID NO:62) of MMP-17/MT4-MMP (matrix metalloproteinase 17, NM_016155).

Figures 35A and 35B show the the nucleic acid sequence (SEQ ID NO:63) and the amino acid sequence (SEQ ID NO:64) of MMP26 (matrix metalloproteinase 26, NM_021801).

Figures 36A and 36B show the nucleic acid sequence (SEQ ID NO:65) and the amino acid sequence (SEQ ID NO:66) of ADAM10 (NM_001110).

Figures 37A and 37B show the nucleic acid sequence (SEQ ID NO:67) and the amino acid sequence (SEQ ID NO:68) of ADAM1 (XM_132370).

Figures 38A and 38B show the nucleic acid sequence (SEQ ID NO:69) and the amino acid sequence (SEQ ID NO:70) of TIM1(NM_003254).

Figures 39A and 39B show the nucleic acid sequence (SEQ ID NO:71) and the amino acid sequence (SEQ ID NO:72) of MUC1 (XM_053256).

Figures 40A and 40B show the nucleic acid sequence (SEQ ID NO:73) and the amino acid sequence (SEQ ID NO:74) of CEA (NM_004363).

Figures 41A and 41B show the nucleic acid sequence (SEQ ID NO:75) and the amino acid sequence (SEQ ID NO:76) of NCA (NM_002483).

Figures 42A and 42B show the nucleic acid sequence (SEQ ID NO:77) and the amino acid sequence (SEQ ID NO:78) of Follistatin (NM_006350).

Figures 43A and 43B show the nucleic acid sequence (SEQ ID NO:79) and the amino acid sequence (SEQ ID NO:80) of Claudin 1 (NM_021101).

Figures 44A and 44B show the nucleic acid sequence (SEQ ID NO:81) and the amino acid sequence (SEQ ID NO:82) of Claudin 14 (NM_012130).

Figures 45A-45B show the nucleic acid sequence (SEQ ID NO:83) and Figure 45C show the amino acid sequence (SEQ ID NO:84) of Tenascin-R (NM-003285).

Figures 46A and 46B show the nucleic acid sequence (SEQ ID NO:85) and the amino acid sequence (SEQ ID NO:86) of CAD3 (NM_001793).

Figures 47A and 47B show the nucleic acid sequence (SEQ ID NO:87) and the amino acid sequence (SEQ ID NO:88) of CONT (NM_001843).

Figures 48A and 48B show the nucleic acid sequence (SEQ ID NO:89) and the amino acid sequence (SEQ ID NO:90) of Osteopontin (NM_000582).

Figures 49A and 49B show the nucleic acid sequence (SEQ ID NO:91) and the amino acid sequence (SEQ ID NO:92) of Galectin 8 (NM_006499).

Figures 50A and 50B show the nucleic acid sequence (SEQ ID NO:93) and the amino acid sequence (SEQ ID NO:94) of GS1 (bihlycan, NM_001711).

Figures 51A and 51B show the nucleic acid sequence (SEQ ID NO:95) and the amino acid sequence (SEQ ID NO:96) of Fizzled 2 (NM001466).

Figures 52A and 52B show the nucleic acid sequence (SEQ ID NO:97) and the amino acid sequence (SEQ ID NO:98) of ISLR (NM_005545).

Figures 53A-53B show the nucleic acid sequence (SEQ ID NO:) and Figure 53C shows the amino acid sequence (SEQ ID NO:2) of

Figures 54A and 54B show the nucleic acid sequence (SEQ ID NO:1) and the amino acid sequence (SEQ ID NO:2) of

Figures 55A and 55B show the nucleic acid sequence (SEQ ID NO:103) and the amino acid sequence (SEQ ID NO:104) of Tie2 ligand2 (NM_001147).

Figures 56A and 56B show the nucleic acid sequence (SEQ ID NO:105) and the amino acid sequence (SEQ ID NO:106) of VEGFC (NM_005429).

Figures 57A and 57B show the nucleic acid sequence (SEQ ID NO:107) and the amino acid sequence (SEQ ID NO:108) of tPA (NM_000930).

Figures 58A-58B show the nucleic acid sequence (SEQ ID NO:109) and Figure 58C shows the amino acid sequence (SEQ ID NO:110) of thrombomodulin (NM_000361).

Figures 59A and 59B show the nucleic acid sequence (SEQ ID NO:111) and the amino acid sequence (SEQ ID NO:112) of TF (coagulation factor III, thromboplastin, tissue factor, NM_0001993).

Figures 60A and 60B show the nucleic acid sequence (SEQ ID NO:113) and the amino acid sequence (SEQ ID NO:114) of GPR4 (G-coupled protein receptor-4, NM_005282).

Figures 61A and 61B show the nucleic acid sequence (SEQ ID NO:115) and the amino acid sequence (SEQ ID NO:116) of GPR66 (G-coupled protein receptor 66).

Figures 62A and 62B show the nucleic acid sequence (SEQ ID NO:117) and the amino acid sequence (SEQ ID NO:118) of SLC22A2 (NM_003058).

Figures 63A-63B show the nucleic acid sequence (SEQ ID NO:119) and Figure 63C shows the amino acid sequence (SEQ ID NO:120) of MLSN1 (NM_002420).

Figures 64A-64B show the nucleic acid sequence (SEQ ID NO:121) and Figure 64C shows the amino acid sequence (SEQ ID NO:122) of ATN2 (Na/K transport, NM_000702).

DESCRIPTION OF THE INVENTION

Barrett's esophagus, a complication of gastrointestinal reflux disease, is the primary risk factor for esophageal adenocarcinoma. Biopsy specimens representing disease progression through Barrett's esophagus, dysplasia and adenocarcinoma, were collected and analyzed using cDNA microarrays to identify genes expressed in the different disease stages. It was discovered that the expression of particular genes increased with the progression of the disease through dysplasia, especially high grade dysplasia, suggestive of a differentiated small intestinal enterocyte lineage. The present invention defines a collection of markers that assist in identifying patients with highest risk of developing cancer, especially the development of esophageal adenocarcinoma.

The progression of Barrett's esophagus through dysplasia to adenocarcinoma was examined, identifying specific genes associated with increasing risk of carcinogenesis. These data provide insight into the potential role of progressive intestinal metaplasia in generating the colon tumor-like expression profiles disclosed herein for esophageal adenocarcinoma. Genes that define early stages of this process, progression of BE to dysplasia, serve as markers to permit targeting of surveillance to those patients at most risk of developing esophageal carcinoma.

DNA microarray technology has been used to characterize and cluster Barrett's metaplasia from normal mucosa, and esophageal adenocarcinoma and squamous cell carcinoma (Barrett et al., Neoplasia 4:121-128 (2002); and Selaru et al., Oncogene 21:475-478 (2002)). The authors do not, however, describe HGD markers or dysplasia markers of any kind useful for predicting patients likely to develop adenocarcinoma.

The present invention provides nucleic acid and protein sequences that are differentially expressed in high-grade esophageal dysplasia when compared to normal tissue controls, here-in termed "high-grade dysplasia genes," "high-grade dysplasia nucleic acid sequences," "HGD marker genes" and the like. As outlined below, high-grade esophageal dysplasia sequences that are differentially expressed include those that are up-regulated in

high-grade esophageal dysplasia). The differential expression of these sequences in high-grade esophageal dysplasia combined with the fact they have been identified in patients likely to develop cancer, such as adenocarcinoma, they are contributory factors in cancer. The high-grade esophageal dysplasia nucleic acid sequences, or the polypeptides encoded by the nucleic acids, of the invention are disclosed in Table 4 as HGD marker genes, or polypeptides, as follows: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44).

Definitions

The phrases "gene amplification" and "gene duplication" are used interchangeably and refer to a process by which multiple copies of a gene or gene fragment are formed in a particular cell or cell line. The duplicated region (a stretch of amplified DNA) is often referred to as "amplicon." Usually, the amount of the messenger RNA (mRNA) produced, *i.e.*, the level of gene expression, also increases in the proportion of the number of copies made of the particular gene expressed.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, adenocarcinoma; lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include esophageal cancer, breast cancer, prostate cancer, colon cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer.

The term "diagnosis" or "diagnosing" as used herein shall refer to the determination of the nature of a case of a disease, such as by determining a gene expression profile or polypeptide expression profile unique to the disease or a stage of the disease.

A "normal" tissue sample refers to tissue or cells that are not diseased as defined herein, such as tissue from a mammal that is not experiencing a particular disease of interest. The term "normal cell" or "normal tissue" as used herein refers to a state of a cell or tissue in which the cell or tissue is apparently free of an adverse biological condition when compared to a diseased cell or tissue having that adverse biological condition. The normal cell or normal tissue may be from any prokaryotic or eukaryotic organism including, but not limited to, bacteria, yeast, insect, bird, reptile, and any mammal including human. Where the normal tissue or cell is used as a normal control sample, it is generally from the same species as the test sample. Where the cell or tissue is mammalian, the cell or tissue is any cell or tissue including, but not limited to blood, muscle, nerve, brain, breast, heart, lung, liver, pancreas, spleen, thymus, esophagus, stomach, intestine, kidney, testis, ovary, uterus, hair follicle, skin, bone, bladder, and spinal cord.

"Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a disorder. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be

prevented. In tumor (*e.g.*, cancer) treatment, a therapeutic agent may directly decrease the pathology of tumor cells, or render the tumor cells more susceptible to treatment by other therapeutic agents, *e.g.*, radiation and/or chemotherapy.

A "pharmaceutical composition" as used herein refers to a composition comprising a chemotherapeutic agent for treatment of a disease combined with physiologically acceptable materials such as carriers, excepients, stabilzers, buffers, salts, antioxidants, hydrophilic polymers, amino acids, carbohydrates, ionic or nonionic uurfactants, and/or polyethylene or propylene glycol. The pharmaceutical composition may be in aqueous form, tablet, capsule, microcapsules, liposomes, trandermal patches, and the like.

The "pathology" of cancer includes all phenomena that compromise the well-being of the patient. This includes, without limitation, abnormal or uncontrollable cell growth, metastasis, interference with the normal functioning of neighboring cells, release of cytokines or other secretory products at abnormal levels, suppression or aggravation of inflammatory or immunological response, etc.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cattle, pigs, sheep, etc. Preferably, the mammal is human.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*, I^{131}, I^{125}, Y^{90} and Re^{186}), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include adriamycin, doxorubicin, epirubicin, 5-fluorouracil, cytosine arabinoside ("Ara-C"), cyclophosphamide, thiotepa, busulfan, cytoxin, taxoids, *e.g.*, paclitaxel (Taxol, Bristol-Myers Squibb Oncology, Princeton, NJ), and doxetaxel (Taxotere, Rhône-Poulenc Rorer, Antony, Rnace), toxotere, methotrexate, cisplatin, melphalan, vinblastine, bleomycin, etoposide, ifosfamide, mitomycin C, mitoxantrone, vincristine, vinorelbine, carboplatin, teniposide, daunomycin, carminomycin, aminopterin, dactinomycin, mitomycins, esperamicins (see U.S. Pat. No. 4,675,187), 5-FU, 6-thioguanine, 6-mercaptopurine, actinomycin D, VP-16, chlorambucil, melphalan, and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors such as tamoxifen and onapristone. In an embodiment, the chemotherapeutic agent of the invention is a chemical compound useful in the treatment of HGD, adenocarcinoma, or for inhibiting or preventing progression from the HGD to adenocarcinoma in a patient.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially cancer cell overexpressing any of the genes identified herein, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent is one which significantly reduces the percentage of cells overexpressing such genes in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel,

eds., Chapter 1, entitled "Cell cycle regulation, oncogens, and antineoplastic drugs" by Murakami *et al.*, (WB Saunders: Philadelphia, 1995), especially p. 13.

"Doxorubicin" is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor-α and -β; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF-β; platelet-growth factor; transforming growth factors (TGFs) such as TGF-α and TGF-β; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon -α, -β, and -γ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL- 1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF-α or TNF-ß; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active parent form. *See, e.g.*, Wilman, "Prodrugs in Cancer Chemotherapy", Biochemical Society Transactions, 14:375-382, 615th Meeting, Belfast (1986), and Stella *et al.*, "Prodrugs: A Chemical Approach to Targeted Drug Delivery", Directed Drug Delivery, Borchardt *et al.*, (ed.), pp. 147-267, Humana Press (1985). The prodrugs of this invention include, but are not

limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glysocylated prodrugs, ß-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrugs form for use in this invention include, but are not limited to, those chemotherapeutic agents described above.

An "effective amount" or therapeutically effective amount" of a polypeptide disclosed herein or an antagonist thereof, in reference to inhibition of neoplastic cell growth, tumor growth or cancer cell growth, is an amount capable of inhibiting, to some extent, the growth of target cells. The term includes an amount capable of invoking a growth inhibitory, cytostatic and/or cytotoxic effect and/or apoptosis of the target cells. An "effective amount" is an amount of an antagonist of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44) gene or polypeptide for purposes of inhibiting neoplastic cell growth, tumor growth or cancer cell growth, may be determined empirically

and in a routine manner. The terms further refer to an amount capable of invoking one or more of the following effects: (1) inhibition, to some extent, of tumor growth, including, slowing down and complete growth arrest; (2) reduction in the number of tumor cells; (3) reduction in tumor size; (4) inhibition (*i.e.*, reduction, slowing down or complete stopping) of tumor cell infiltration into peripheral organs; (5) inhibition (*i.e.*, reduction, slowing down or complete stopping) of metastasis; (6) enhancement of anti-tumor immune response, which may, but does not have to, result in the regression or rejection of the tumor; and/or (7) relief, to some extent, of one or more symptoms associated with the disorder. A "therapeutically effective amount" of an antagonist of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); or TCF4 (NM_030756) (SEQ ID NO:43 or 44) gene or polypeptide for purposes of treatment of tumor may be determined empirically and in a routine manner.

A "growth inhibitory amount" of a compound that inhibits growth of a cell expressing genes, or polypeptides, from the following group: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ

ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44) is an amount of the compound capable of inhibiting the growth of a cell, especially tumor, *e.g.*, cancer cell, either *in vitro* or *in vivo*. Optionally, the compound is an antagonist of the gene or polypeptide, such as an antagonist antibody or antagonist small organic molecule. A "growth inhibitory amount" of such a compound, for purposes of inhibiting neoplastic cell growth, may be determined empirically and in a routine manner.

A "cytotoxic amount" of an ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ

ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide antagonist is an amount capable of causing the destruction of a cell, especially tumor, *e.g.*, cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of a such a polypeptide antagonist for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

The terms ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); and TCF4 (NM_030756) (SEQ ID NO:44) polypeptide or protein when used herein encompass native sequence ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20);

PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); and TCF4 (NM_030756) (SEQ ID NO:44) polypeptide variants (which are further defined herein). The ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant and/or synthetic methods.

A "native sequence polypeptide" of each HGD marker polypeptide has the same amino acid sequence or is a polypeptide variant having at least about 80% amino acid sequence identity, preferably at least about 81% amino acid sequence identity, more preferably at least about 82% amino acid sequence identity, more preferably at least about 83% amino acid

sequence identity, more preferably at least about 84% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, more preferably at least about 86% amino acid sequence identity, more preferably at least about 87% amino acid sequence identity, more preferably at least about 88% amino acid sequence identity, more preferably at least about 89% amino acid sequence identity, more preferably at least about 90% amino acid sequence identity, more preferably at least about 91% amino acid sequence identity, more preferably at least about 92% amino acid sequence identity, more preferably at least about 93% amino acid sequence identity, more preferably at least about 94% amino acid sequence identity, more preferably at least about 95% amino acid sequence identity, more preferably at least about 96% amino acid sequence identity, more preferably at least about 97% amino acid sequence identity, more preferably at least about 98% amino acid sequence identity and most preferably at least about 99% amino acid sequence identity with a full-length native sequence polypeptide sequence, lacking the signal peptide as disclosed herein, as the ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide as derived from nature. Such native sequence polypeptide can be isolated from nature or can be produced by recombinant and/or synthetic means. The term "native sequence polypeptide" specifically encompasses naturally-occurring truncated or secreted forms (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and

naturally-occurring allelic variants of the polypeptides encoded by a HGD marker gene as disclosed herein. In one embodiment of the invention, the native sequence HGD marker polypeptide is a mature or full-length native sequence HGD marker polypeptide as encoded by the nucleic acid sequences of the GenBank accession numbers listed in Table 4A for the respective polypeptide. Also, the HGD marker polypeptides encoded by the nucleic acid sequences disclosed in the respective GenBank accession numbers listed in Table 4A, are shown to begin with the methionine residue designated therein as amino acid position 1, it is conceivable and possible that another methionine residue located either upstream or downstream from amino acid position 1 may be employed as the starting amino acid residue for HGD marker polypeptide.

The "extracellular domain" or "ECD" of a polypeptide disclosed herein refers to a form of the polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a polypeptide ECD will have less than about 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than about 0.5% of such domains. It will be understood that any transmembrane domain(s) identified for the polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified and as shown in the appended figures. As such, in one embodiment of the present invention, the extracellular domain of a polypeptide of the present invention comprises amino acids 1 to X of the mature amino acid sequence, wherein X is any amino acid within 5 amino acids on either side of the extracellular domain/transmembrane domain boundary.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (*e.g.*, Nielsen *et al.*, Prot. Eng., 10:1-6 (1997) and von Heinje *et al.*, Nucl. Acids. Res., 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one

secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

A "polypeptide variant" of any one of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length HGD marker polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a HGD marker polypeptide variant will have at least about 80% amino acid sequence identity, preferably at least about 81% amino acid sequence identity, more preferably at least about 82% amino acid sequence identity, more preferably at least about 83% amino acid sequence identity, more preferably at least about 84% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, more preferably at least about 86% amino acid sequence identity, more preferably at least about 87% amino acid sequence identity, more preferably at least about 88% amino acid sequence identity, more preferably at least about 89% amino acid sequence identity, more preferably at

least about 90% amino acid sequence identity, more preferably at least about 91% amino acid sequence identity, more preferably at least about 92% amino acid sequence identity, more preferably at least about 93% amino acid sequence identity, more preferably at least about 94% amino acid sequence identity, more preferably at least about 95% amino acid sequence identity, more preferably at least about 96% amino acid sequence identity, more preferably at least about 97% amino acid sequence identity, more preferably at least about 98% amino acid sequence identity and most preferably at least about 99% amino acid sequence identity with a full-length native sequence polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a HGD marker polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length HGD marker polypeptide sequence as disclosed herein. Ordinarily, a HGD marker polypeptide variant is at least about 10 amino acids in length, often at least about 20 amino acids in length, more often at least about 30 amino acids in length, more often at least about 40 amino acids in length, more often at least about 50 amino acids in length, more often at least about 60 amino acids in length, more often at least about 70 amino acids in length, more often at least about 80 amino acids in length, more often at least about 90 amino acids in length, more often at least about 100 amino acids in length, more often at least about 150 amino acids in length, more often at least about 200 amino acids in length, more often at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the amino acid sequence of any of the HGD marker polypeptides identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in an ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID

NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 5. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 5 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 5. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid

sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations, Tables 2A-2B demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO".

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

In addition, % amino acid sequence identity may also be determined using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to

default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acids residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (*i.e.*, the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an amino acid sequence A which has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

As used herein, a "HGD marker" or "cancer marker gene or polypeptide," or "anti-[HGD marker]" or "anti-[cancer marker]" refers to any one of the genes, polypeptides encoded by the genes, or antibodies specific for the polypeptides described herein as diagnositic for HGD or cnacer. Thus, for example, "TCF4" refers to the gene marker or its encoded polypeptide, whereas anti-TCF4 refers to an antobidy to the TCF4-encoded polypeptide.

A "gene variant polynucleotide" as used herein refers to a nucleic acid sequence that varies from the native sequence of its respective HGD marker gene NCBI accession sequence as disclosed in Table 4A, and further refers to a nucleic acid molecule which encodes a biologically active polypeptide and which nucleic acid molecule has at least about 80% nucleic acid sequence identity with a nucleic acid sequence selected from the group of marker genes: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769)

(SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), which genes encode, respectively, the full-length native polypeptides of the group: ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); and TCF4 (NM_030756) (SEQ ID NO:44) polypeptide sequence as disclosed herein, a full-length native sequence HGD marker polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a HGD marker polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length HGD marker polypeptide sequence as disclosed herein. Ordinarily, a HGD marker variant polynucleotide will have at least about 80% nucleic acid sequence identity, more preferably at least about 81% nucleic acid sequence identity, more preferably at least about 82% nucleic acid sequence identity, more preferably at least about 83% nucleic acid sequence identity, more preferably at least about 84% nucleic acid sequence identity, more preferably at

least about 85% nucleic acid sequence identity, more preferably at least about 86% nucleic acid sequence identity, more preferably at least about 87% nucleic acid sequence identity, more preferably at least about 88% nucleic acid sequence identity, more preferably at least about 89% nucleic acid sequence identity, more preferably at least about 90% nucleic acid sequence identity, more preferably at least about 91% nucleic acid sequence identity, more preferably at least about 92% nucleic acid sequence identity, more preferably at least about 93% nucleic acid sequence identity, more preferably at least about 94% nucleic acid sequence identity, more preferably at least about 95% nucleic acid sequence identity, more preferably at least about 96% nucleic acid sequence identity, more preferably at least about 97% nucleic acid sequence identity, more preferably at least about 98% nucleic acid sequence identity and yet more preferably at least about 99% nucleic acid sequence identity with the nucleic acid sequence encoding a full-length native sequence HGD marker polypeptide sequence as disclosed herein, a full-length native sequence HGD marker polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a HGD marker polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length HGD marker polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, HGD marker gene variant polynucleotides are at least about 20 nucleotides in length, frequently at least about 30 nucleotides in length, often at least about 60 nucleotides in length, more often at least about 90 nucleotides in length, more often at least about 120 nucleotides in length, more often at least about 150 nucleotides in length, more often at least about 180 nucleotides in length, more often at least about 210 nucleotides in length, more often at least about 240 nucleotides in length, more often at least about 270 nucleotides in length, more often at least about 300 nucleotides in length, more often at least about 450 nucleotides in length, more often at least about 600 nucleotides in length, more often at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to variant polypeptides of each of the HGD marker polypeptide-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in a HGD marker polypeptide-encoding nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be

achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % nucleic acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 5. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 5 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 5. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 2C-2D demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA".

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer

program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In addition, % nucleic acid sequence identity values may also be generated using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (*i.e.*, the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the

PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, variants of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); or TCF4 (NM_030756) (SEQ ID NO:43) HGD marker genes encode an active HGD marker polypeptide, and nucleic acid sequences useful for identifying the marker genes by, for example, nucleic acid hybridization assays or PCR assays are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta,

NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43) gene or hybridizable fragments thereof, which nucleotide sequences are found in the NCBI accession numbers listed in Table 4A for the respective polypeptides. HGD variant polypeptides may be those that are encoded by a HGD marker gene variant polynucleotide.

The term "positives", in the context of the amino acid sequence identity comparisons performed as described above, includes amino acid residues in the sequences compared that are not only identical, but also those that have similar properties. Amino acid residues that score a positive value to an amino acid residue of interest are those that are either identical to the amino acid residue of interest or are a preferred substitution (as defined in Table 4A below) of the amino acid residue of interest.

For purposes herein, the % value of positives of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % positives to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scoring a positive value as defined above by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % positives of A to B will not equal the % positives of B to A.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide's natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" nucleic acid molecule encoding an ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID

NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptide or an "isolated" nucleic acid encoding an anti-[HGD marker polypeptide] antibody, is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the HGD marker genes or the anti-[HGD marker polypeptide]-encoding nucleic acid. Preferably, the isolated nucleic acid is free of association with all components with which it is naturally associated. An isolated polypeptide or nucleic acid sequence is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule encoding a HGD maker polypeptide or an anti-[HGD marker polypeptide] antibody includes HGD marker gene nucleic acid molecules and anti-[HGD marker polypeptide]-encoding nucleic acid molecules contained in cells that ordinarily express HGD marker polypeptides or express anti-[HGD maker polypeptide] antibodies where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence,

and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-[HGD marker polypeptide] monoclonal antibodies (including antagonist, and neutralizing antibodies), anti-[HGD marker polypeptide] antibody compositions with polyepitopic specificity, single chain anti-[HGD marker polypeptide] antibodies, and fragments thereof (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional

details and explanation of stringency of hybridization reactions, *see* Ausubel *et al.*, Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 □g/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (*e.g.*, temperature, ionic strength and % SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 35□C-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a HGD marker polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino

acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" for the purposes herein refers to form(s) of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:4); ADAM8 (NM_001109) (SEQ ID NO:6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:12); TM7SF1 (NM_003272) (SEQ ID NO:14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NO:16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:42); or TCF4 (NM_030756) (SEQ ID NO:44) polypeptides which retain a biological and/or an immunological activity/property of a native or naturally-occurring HGD marker polypeptide, wherein "biological" activity refers to a function (either inhibitory or stimulatory) caused by a native or naturally-occurring HGD marker polypeptide other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring HGD marker polypeptide and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring HGD marker polypeptide.

"Biological activity" in the context of an antibody or another antagonist molecule, or therapeutic compound that can be identified by the screening assays disclosed herein (*e.g.*, an organic or inorganic small molecule, peptide, etc.) is used to refer to the ability of such molecules to bind or complex with the polypeptides encoded by the amplified genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other

cellular proteins or otherwise interfere with the transcription or translation of a HGD marker polypeptide. "Biological activity" in the context of an agonist molecule that enhances the activity of, for example, native anti-angiogenic molecules refers to the ability of such molecules to bind or complex with the polypeptides encoded by the amplified genes identified herein or otherwise modify the interaction of the encoded polypeptides with other cellular proteins or otherwise enhance the transcription or translation of a TIMP1 or thrombospondin 2 polypeptide. A preferred biological activity is growth inhibition of a target tumor cell. Another preferred biological activity is cytotoxic activity resulting in the death of the target tumor cell.

The term "biological activity" in the context of a HGD marker polypeptide means the typical activity of the HGD marker polypeptide in the cell.

The phrase "immunological activity" means immunological cross-reactivity with at least one epitope of a HGD marker polypeptide.

"Immunological cross-reactivity" as used herein means that the candidate polypeptide is capable of competitively inhibiting the qualitative biological activity of a HGD marker polypeptide having this activity with polyclonal antisera raised against the known active HGD marker polypeptide. Such antisera are prepared in conventional fashion by injecting goats or rabbits, for example, subcutaneously with the known active analogue in complete Freund's adjuvant, followed by booster intraperitoneal or subcutaneous injection in incomplete Freunds. The immunological cross-reactivity preferably is "specific", which means that the binding affinity of the immunologically cross-reactive molecule (*e.g.*, antibody) identified, to the corresponding HGD marker polypeptide is significantly higher (preferably at least about 2-times, more preferably at least about 4-times, even more preferably at least about 8-times, most preferably at least about 10-times higher) than the binding affinity of that molecule to any other known native polypeptide.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native HGD marker polypeptide disclosed herein or the transcription or translation thereof, particularly when the HGD marker polypeptide is expressed about 1.5-fold above the level of expression in normal tissue controls. Suitable antagonist molecules specifically include antagonist antibodies or

antibody fragments, binding fragments, peptides, small organic molecules, anti-sense nucleic acids, etc. Included are methods for identifying antagonists of an ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44) gene or polypeptide with a candidate antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1 or 2); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3 or 4); ADAM8 (NM_001109) (SEQ ID NO:5 or 6); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7 or 8); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9 or 10); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11 or 12); TM7SF1 (NM_003272) (SEQ ID NO:13 or 14); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15 or 16); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17 or 18); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19 or 20); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21 or 22); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23 or 24); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25 or 26); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27 or 28); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID

NO:29 or 30); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31 or 32); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33 or 34); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35 or 36); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37 or 38); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39 or 40); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41 or 42); and TCF4 (NM_030756) (SEQ ID NO:43 or 44) gene or polypeptide.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

"Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules which lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) formed from at least two intact antibodies, and antibody fragments so long as they exhibit the desired biological activity.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework (FR) regions. The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (*see* Kabat *et al.*, NIH Publ. No.91-3242, Vol. I, pages 647-669 (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (*i.e.*, residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institute of Health, Bethesda, MD. [1991]) and/or those residues from a "hypervariable loop" (*i.e.*, residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain ; Clothia and Lesk, J. Mol. Biol., 196:901-917 [1987]). "Framework" or "FR" residues are those variable domain residues other than the hypervariable region residues as herein defined.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata *et al.*, Protein Eng. , 8(10):1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, Nature, 256:495 [1975], or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352:624-628 [1991] and Marks *et al.*, J. Mol. Biol., 222:581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 [1984]).

"Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat

or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see*, Jones *et al.*, Nature, 321:522-525 (1986); Reichmann *et al.*, Nature, 332:323-329 [1988]; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992). The humanized antibody includes a PRIMATIZED™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv *see* Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H - V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the

antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (*e.g.*, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable. Radionuclides that can serve as detectable labels include, for example, I-131, I-123, I-125, Y-90, Re-188, Re-186, At-211, Cu-67, Bi-212, and Pd-109. The label may also be a non-detectable entity such as a toxin.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a CXCR4; Laminin alpha 4; TIMP1; Type IV collagen alpha 1; Laminin alpha 3; Adrenomedullin; Thrombospondin 2; Type I collagen alpha 2; Type VI collagen alpha 2; Type VI collagen alpha 3; Latent TGFbeta binding protein 2 (LTBP2); Serine or cystein protease inhibitor heat shock protein (HSP47); Procollagen-lysine, 2-oxoglutarate 5-dioxygenase; connexin 43; Type IV collagen alpha 2; Connexin 37; Ephrin A1; Laminin beta 2; Integrin alpha 1; Stanniocalcin 1; Thrombospondin 4; or CD36 polypeptide or antibody thereto and, optionally, a chemotherapeutic agent) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an

immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Up-regulation," "increased expression," and "overexpression" are used interchangeably and, as used herein, mean at least about a 1.5-fold increase in expression, alternatively at least about a 2-fold increase in expression, alternatively with at least about a 2.5-fold or higher increase in expression of a gene measured as an increase in its DNA (amplification), its mRNA (increased transcription), or in the level of polypeptide encoded by the gene. Alternatively, up-regulation or increased expression is determined using a Z score as a p value < 0.07 relative to a normal tissue control.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

It will be clearly understood that, although a number of art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Throughout this specification and the claims, the terms "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

EXAMPLES

The following examples are offered by way of illustration and not by way of limitations. The examples are provided so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the compounds, compositions, and methods of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to insure accuracy with respect to numbers used (e.g. amounts, temperature, etc. but some experimental errors and deviation should be

accounted for. Unless indicated otherwise, parts are in parts by weight, temperature is in degrees C, and pressure is at or near atmospheric. The disclosures of all citations in the specification are expressly incorported herein by reference.

Example 1: Patients and Tissue Collection

Esophageal mucosal biopsies were obtained from patients undergoing surveillance endoscopy at the Western General Hospital and Royal Infirmary, Edinburgh during 2000-1. The study was approved by the Lothian Research and Ethics Committee and written, informed consent was obtained from all patients. All procedures were performed by one of two experienced endoscopists with expertise in Barrett's esophagus in a standard manner according to a local protocol for Barrett's surveillance. BE was defined as tongues or circumferential salmon pink mucosa extending for at least 3cm above the gastro-esophageal junction. At endoscopy, careful note was made of the length of the CE segment, severity of any esophagitis if present and the presence of macroscopically visible abnormalities within the BE. Data on smoking history, use of acid-suppressing drugs and *Helicobacter pylori* status were also recorded.

Paired biopsies were taken. One sample was fixed in formalin for histology and the other stored fresh-frozen (-70°C) for microarray analysis. Two gastrointestinal pathologists reviewed all specimens, which were categorized as: normal squamous esophagus, BE (columnar lined esophagus with intestinal metaplasia and the presence of goblet cells and alcian blue positive mucin), BE with changes indeterminate dysplasia, BE with low-grade dysplasia (LGD), BE with high-grade dysplasia (HGD) or BE with adenocarcinoma (CA). For some patients, 2 separate biopsy specimens for the same disease state were available for array analysis. Additional matched samples were also analyzed (*e.g.* biopsies of BE adjacent to carcinoma in BE from the same patient). Analyzed samples included 10 normal esophagus, 28 samples of BE from 20 patients, 6 samples of LGD from 3 patients, 3 samples indeterminate for dysplasia from 2 patients, 6 samples HGD from 3 patients, 10 samples of BE adjacent to CA (BE-CA) from 7 patients, 16 samples CA from 10 patients.

Microarrays containing 9031 genes were generated by printing PCR products derived from cDNA clones (Invitrogen, California and Genentech, Inc.) on glass slides coated with 3-aminopropyltriethoxysilane(Aldrich, Milwaukee WI) and 1,4-phenylenediisothiocyanate (Aldrich, Milwaukee WI) using a robotic arrayer (Norgren Systems, Mountain View,

California). RNA isolation was accomplished by CsCl step gradient, (Kingston, Current Protocols in Molecular Biology 1:4.2.5-4.2.6 (1998)) typically 0.1 – 2 μg of total RNA was obtained. Probes for array analysis were generated by conservative amplification and subsequent labelling as follows: double-stranded DNA generated from 0.1 μg of total RNA (Invitrogen, Carlsbad, CA) was amplified using a single round of a modified in vitro transcription protocol (MEGASCript T7 from Ambion, Austin, Texas (Gelder et al., Proc. Natl. Acad. Sci. USA 87:1663-1667 (1990)). The resulting cRNA was used as a template to generate a sense DNA probe using random primers (9mers, 0.15 mg/ml), Alexa 488 dUTP or Alexa 546 dUTP (40 μM and 6 μM, respectively, Molecular Probes, Eugene, Oregon) using MMLV-derived reverse transcriptase (Invitrogen, Carlsbad, CA). A reference probe to reflect general epithelial cell expression was generated from 0.1 μg of total RNA from a pool of liver, lung and kidney (Clontech, Palo Alto, California). Probes were hybridized to arrays overnight in 50% formamide / 5XSSC at 37 °C and washed the next day in 2XSSC, 0.2% SDS followed by 0.2XSSC, 0.2% SDS. Array images were collected using a CCD-camera based imaging system (Norgren Systems, Mountain View, California) equipped with a Xenon light source and optical filters appropriate for each dye. Full dynamic-range images were collected (Autograb, Genentech Inc) and intensities and ratios extracted using automated gridding and data extraction software (gImage, Genentech Inc) built on a Matlab (the MathWorks, Natick, Massachusetts) platform.

Example 3: Data Analysis

Data were sorted to identify genes expressed above background (N intensity of > 12 where background values range from 0 – 8) in the test sample such that only meaningful ratios were included. Ratio values were further normalized for experimental scatter at different intensity values within each experiment by plotting log ratio versus N intensity and by fitting a normal distribution at each intensity level. A measure of standard deviation (Z score) around a mean of zero was derived for each gene in each experiment and this value was used in data mining. Specifically, for each microarray, data were normalized by computing Z-scores, which were obtained from a scatterplot of the logarithm of the ratio of the test and reference data versus the logarithm of the minimum of the test and reference data. The median of the ratio as a function of intensity was estimated by applying the loess algorithm to the scatterplot. The standard error was estimated by applying loess to the square root of the absolute residuals, and squaring the result to obtain the median absolute deviation (MAD), and making a

multiplicative correction to convert from MAD to a standard error. The Z scores were determined for each ratio by dividing its vertical distance from the median loess curve by the standard error at that intensity.

A computational process useful computing Z-scores may be written in a standard high-level statistical language, S-Plus, as follows:

```
pos.test <- test[test > 0 & ref > 0]
pos.ref <- ref[test > 0 & ref > 0]
minorder <- order(pmin(pos.test,pos.ref))
y <- log(pos.test[minorder] + 10) - log(pos.ref[minorder] + 10)
x <- log(pmin(pos.test[minorder],pos.ref[minorder]))
residuals <- loess(y ~ x)$residuals
sqresiduals <- sqrt(abs(residuals))
sqrt.mad <- loess(sqresiduals ~ x)$fitted
sigma <- sqrt.mad*sqrt.mad/0.6745
zscore <- ifelse(sigma > 0,residuals/sigma,0)
```

This code may be executed in a commercially available S-Plus program such as, for example, (http://www.insightful.com), or in a freely available substituteprogram, R (http://www.r-project.org).

Example 4: Differential Expression in Barrett's Esophagus-to-Adenocarcinoma Disease Stages

Samples and Data Mining:

High-quality data were obtained from > 90% of biopsy specimens, including those of poor RNA quality and very limited RNA quantity (eg. less than 200 ng total RNA). A data mining strategy was applied to identify genes specifically associated with the different stages of disease progression. Experiments were grouped into disease categories based on pathologic diagnosis, and these groups compared to identify genes with significant elevated expression for at least 25% of the samples within a disease group with respect to both the epithelial pool reference and the normal esophagus group. Typically, genes with elevated expression were

identified as those with Z scores of > 1.7 ($p < 0.05$) in the disease group, corresponding to ratio values of 2 – 20 in most cases. A total of 460 genes satisfied these criteria across the disease groups BE, dysplasia, and carcinoma (some genes are associated with more than one disease group). Selected genes (117) are listed (Tables 1, 2, 3). All dysplasia samples (high-, low-grade and indeterminate) were combined into a single group to improve data analysis, and the genes identified were then further inspected to determine if they were more prevalent in low- or high-grade dysplasia. HGD sample data were independently analyzed to determine gene expression profiles diagnostic for high-grade dysplasia (Table 4A).

Inflammation:

Significant expression of proinflammatory, costimulatory and inducible cytokines and receptors was observed in BE, dysplasia and carcinoma, and the most prevalent genes are listed (Table 1). Some binding partners were detected, such as putative inflammatory cytokine IL-17 family member IL-17E and its receptor IL-17BR, and SCYA20/LARC and receptor CCR6 (Lee et al., J. Biol. Chem. 276:1660-1664 (2001); and Baba et al., J. Biol. Chem. 272:14893-14898 (1997)). SCYA20 is expressed in the epithelium of the small intestine and is chemotactic for lymphocytes and dendritic cells (Tanaka et al., Eur. J. Immunol. 29:644-642 (1999)). Activin A is a TGF beta superfamily member that can act as a potent mediator of cell growth and differentiation and may be involved in response to injury (Munz et al., EMBO J. 18:5205-5215 (1999)). It was co-expressed particularly in carcinoma in Barrett's samples with its serine-threonine kinase receptor AVRII (the type I receptor was also detected but less well correlated). Chemokine receptors CXCR4 and CCR7 have been detected on a variety of inflammatory cell types, but have also been described has highly expressed in breast tumor cells, with possible involvement in lymph node metastasis (Muller et al., Nature 410:50-56 (2001)). In this study, CXCR4 in particular was associated with high-grade dysplasia and detected in some samples of adenocarcinoma.

TABLE 1A Cytokines and chemokines up-regulated in BE-to-Adenocarcinoma

NCBI RefSeq	Gene	BE	D	BE-CA	CA
NM_000594	TNF-a	*		*	*
NM_002546	Osteoprotegerin	*		*	
NM_002993	GCP-2	(*)	* H	(*)	*
NM_025240	B7-H3		* L	(*)	*
NM_002995	Lymphotactin	(*)	*		(*)
NM_005746	PBEF	*			(*)
NM_004591	SCYA20		(*)	*	
NM_004843	WSX1		*		
NM_019618	IL1-H1	(*)		*	*
NM_000418	IL-4R				*
NM_022789	IL-17E	(*)	*	*	*
NM_018725	IL-17BR		* H		(*)
NM_014432	IL-20Ra		* L		(*)
NM_021798	IL-21R	(*)		*	*
NM_002192	Activin A		(*)	(*)	*
NM_001616	AVR2, type II activin receptor		*		*
NM_001105	Activin A type I Receptor				(*)
NM_031409	CCR6	(*)		*	*
NM_003467	CXCR4		* H		(*)
NM_001838	CKR7	(*)	(*)	*	

TABLE 1B Prostaglandin synthesis-related genes up-regulated in BE-to-Adenocarcinoma

NCBI RefSeq	Gene	BE	D	BE-CA	CA
NM_000963	COX-2, prostaglandin synthase 2	(*)	* H		*
NM_000962	COX-1, prostaglandin synthase 1				*
NM_007366	PLA2R phosphlipase A2 R1		*	(*)	*
NM_000953	PD2R prostaglandin D2 R	(*)		(*)	*
NM_000959	PF2AR prostaglandin F2α R		*	(*)	(*)
NM_000957	PER3 prostaglandin E R 2			(*)	*
NM_000960	Prostaglindin IP (I2) R	*	*	(*)	

Genes are associated with the disease states B3, dysplasia (D), BE adjacent to carcinoma (BE-CA), or carcinoma (CA) if present in at least 25% of samples tested. (*) indicates gene expression changes associated wiht 15-25% of samples.

An otherwise rare IL-1 homolog, IL1-H1, was highly expressed in carcinoma in Barrett's, and also the matched adjacent BE tissue from the same patients (Fig. 1). A previous study of the murine Il-1H1 ortholog detected constitutive only in esophageal squamous mucosa. In addition, human IL1-H1 mRNA could be induced in TNF□ and IFN□ treated keratinocytes and squamous epithelial tumor cell line A431 (Kumar et al., J. Biol. Chem. 275:10308-10314 (2000)). This gene is one marker of a specific esophageal squamous cell type exhibiting a striking induction of expression in both adenocarcinoma and patient-matched BE, amidst primarily intestinal and tumor markers observed in this study (Tables 2 and 3). The high expression in BE matched with adenocarcinoma in addition to adenocarcinoma suggests a possible epigenetic association.

Cylooxyengase isoform 2 (COX-2), which catalyzes a rate-limiting step in conversion of arachidonate to inflammatory prostaglandins, has been implicated in Barrett's metaplasia and other cancers (Morris et al., Am. J. Gastroenterol. 96:990-996 (2001); Heasley et al., J. Biol. Chem. 272:14501-14504 (1997); and Tsujii et al., Cell 93:705-716 (1998)). Consistent with previous reports, a significant increase was observed in COX-2 gene expression with increasing dysplasia (high-grade dysplasia) and in adenocarcinoma (Table 1B). Smaller changes were also observed in COX-1 and several prostaglandin receptors. Arachidonic acid is released from the membrane by the action of phospholipases. Phospholipase A2 expression associated with increasing malignancy was also observed (Table 2) along with the M-type receptor (PLA2R, Table 1B), consistent with studies suggesting that COX-2, PA2 and PLA2R are coordinately expressed (Rys-Sikora et al., Am. Physiol. Cell Physiol. 278:822-833 (2000)).

Elevated expression was detected for another enzyme that generates a different class of biologically active eicosanoids from arachidonic acid, the epoxygenase CYP2J2 (Fig. 1B, Table 2). This cytochrome P450 enzyme is expressed in a variety of cell types in the small intestine, including epithelial cells, and may play a role in electrolyte transport, intestinal motility, and other processes (Wu et al., J. Biol. Chem. 271:3460-3468 (1996); Zeldin et al., Mol. Pharm. 51:931-943 (1997); and Node et al., Science 285:1276-1279 (1999)). Similar to COX-2, elevated expression is most apparent in samples of adenocarcinoma and dysplasia

(both low-grade and high-grade dysplasia). The expression profile for CYP2J2 also reflects the progressive intestinal metaplasia observed in this study (Table 2).

Intestinal Metaplasia:

Analysis for gene expression changes associated with dysplasia revealed a large group of genes whose normal expression is primarily associated with the small intestine, and to a lesser extent, colon (Table 2). The previously described marker villin was detected, (Peterson and Moosekar, J. Cell Sci. 102:581-600 (1992)) along with a diverse set of genes including cell surface cadherins and claudins, ion channels and transporters, and enzymes, many of which are normally associated with structural and absorptive functions of small intestinal villi. Increased expression of many of these genes was associated with dysplasia and a significant subset of carcinoma samples, with differential expression also detected in a smaller subset of BE samples. Furthermore, expression of the majority of genes was less prevalent in matched BE samples taken from the carcinoma patients, even when expression was apparent in the tumor sample (Fig. 2A, 2B, 3A; Table 2). This suggests that these gene expression changes are more specifically associated with the foci of dysplasia and developing carcinoma within the larger region of BE.

TABLE 2 Genes up-regulated in intestinal metaplasia

NCBI RefSeq	SEQ ID NOS (na and aa)	Gene	Gene Description	BE	D	BE-CA	CA	Normal Tissues
NM_007127		Villin 1	actin binding protein	*	*	*	*	SI, C
NM_003379		Villin 2	actin binding protein	*				SI, St, C, O
NM_000775	35 and 36	CYP2J2	arachidonic acid epoxygenase		*	(*)	*	SI, L, H
NM_005379	33 and 34	MYO1A	myosin 1A		* H		*	SI (C)
NM_004063	45 and 46	CAD17	liver-intestine cadherin	(*)	(* H)	(*)	*	SI, C
NM_017717		MUCDHL	mucin and cadherin like			*		SI (C, K)
NM_014343	47 and 48	CLDN15	claudin 15	(*)	* L	(*)	*	SI
NM_012132		CLDN8	claudin 8		*		(*)	C, K
NM_005567		IR-95	lectin-binding			(*)	*	C, SI, St, O
NM_000021		Presenilin-1	beta-catenin binding		* H		(*)	SI, C
NM_003039		GLUT5	glucose transporter	*	(*)		(*)	SI
NM_001081		CUBN	transport (HDL, vit.B12, etc)		* L			K, SI
NM_004769	23 and 24	SLNAC1	sodium channel		* H	*	*	CNS, SI, O
NM_000492	49 and 50	CFTR	chloride channel	*	(* H)		*	P, SI, C
NM_003272	13 and 14	TM7SF1	novel GPCR	(*)	* H			K, C, SI, O
NM_005242	29 and 30	PAR2 / F2RL1	GPCR, proteinase-activated		* H			SI, C
NM_022304	51 and 52	H2R	histamine H2 receptor	(*)	*	*	*	St-par
NM_004624		VIPR1	intestinal peptide GPCR			*		L, SI, C, CNS

NM_002773	7 and 8	PRSS8	serine protease			*	*	SI, C, St
NM_058186		RPLA320	novel		* L	(*)		SI (St, C, P)
NM_003561		SPLA2	phosphlipase A2 group X		*	(*)	(*)	C, St, SI
NM_000928	27 and 28	PA21	phospholipase A2 group IB		*	(*)	*	P, SI, C
NM_001631	21 and 22	PPBI	intestinal alkaline phosphatase	(*)	*			SI
NM_000717	25 and 26	CAH4	carbonic anhydrase IV		* H		(*)	C, SI
NM_005763		LKR/SDH	lysine catabolism	(*)	* H		*	SI, C, O
NM_004969	31 and 32	IDE	insulin degrading enzyme	(*)	*	*	*	SI-ent., O
NM_001914	39 and 40	CYB5	cytochrome B5	(*)	* H		(*)	L, SI, K
NM_001863	41 and 42	COX6B	cytochrome C oxidase subunit	(*)	* H		*	H, M, SI, C, St
NM_000108	15 and 16	DLDH	dihydrolipamide dehydrogenase	(*)	*			H, M, K; SI, C
NM_006214	37 and 38	PHYH	phytanoyl-CoA hydroxylase		* H			L, K, M; SI, C
NM_013283	17 and 18	MAT2B	methionine adenosyltransferase		* H	(*)	(*)	SI, C, O
NM_000414		BHSD	hydroxysteroid dehydrogenase			(*)	*	L, SI, O
NM_005038		cyclophilin-40	peptidyl prolyl isomerase		* L		*	SI, C, L, M
NM_138393		DP1	membrane trafficking		(*)	*	*	L, SI
NM_006408	3 and 4	AGR2	anterior gradient 2 homolog		* H		*	St, SI, C
NM_021969	11 and 12	NROB2	nuclear hormone receptor	*	* H		*	SI, L, St
NM_005524		Hes1	transcriptional regulator	*	* H	*	*	SI-ent., O
NM_002054		GCG	proglucagon		(*)		*	P, SI, C

Genes are associated with the disease states B3, dysplasia (D), BE adjacent to carcinoma (BE-CA), or carcinoma (CA) if present in at least 25% of samples tested. (*) indicates gene expression changes associated wiht 15-25% of samples.

Normal Tissues: highest normal tissue expression is listed. SI (small intestine); C (colon); St (stomach); K (kidney); P (pancreas); L (liver); M (muscle); H (heart); CNS (central nervous system); SI-ent (intestinal enterocytes); St-par (parietal cells; O (other tissues). In the dysplasia column, H or L denote expression associated with high-grade or low-grade dysplasia, respectively. GPCR (G protein coupled receptor). "na" and "aa" refer to the nucleic acid and amino acid SEQ ID NO, respectively, for the associated markers.

Examples include MYO1A, an unconventional myosin that is differentially expressed along with crypt-villus axis, exhibiting low level cytosolic expression in immature crypts and high expression in villus cells with localization at the brush border (Skowron et al., Cell Motil Cytoskel. 41:308-324 (1998); and MacLennan et al., Molec. Carcinogen. 24:137-143 (1999)). Unlike villin, another marker of the brush border that was detected across all disease states, MYO1A was most associated with high-grade dysplasia and carcinoma. The novel secreted factor AGR2 gives one of the most striking profiles as a marker for high-grade dysplasia (Figure 2A). AGR2 is a human homolog of the *X. laevis* cement gland gene XAG-2, which is implicated in ectodermal patterning (Aberger et al., Mech. Dev. 72:115-130 (1998)). Elevated expression of this gene is also associated with hormonally-responsive high-grade esophageal dysplasias (Thompson and Weigel, Biochem. Biophys. Res. Commun. 251:111-116 (1998)).

Expression of nuclear hormone receptor NROB2 is induced by bile acids, and NROB2 in turn participates in transcriptional repression of the rate-limiting enzyme (CYP7A1) in bile synthesis (Lu et al., Mol. Cell 6:507-515 (2000)). In this study, overexpression of NROB2 is detected in particularly in high-grade dysplasia, in addition to some carcinomas and a subset of BE samples (Figure 2B). In addition to supporting the general pattern of intestinal metaplasia, expression of NROB2 may further reflect the response to the unnatural exposure of esophageal cells to bile, which is considered to be a contributing factor in Barrett's metaplasia (Bremner et al, Surgery 68:209-216 (1970); and Gillen et al., Br. J. Surg. 75:1352-1355 (1988)). Bile acids have also been shown to activate transcription of COX-2 (Zhang et al., J. Biol. Chem. 273:2424-2428 (1998)).

While these gene expression profiles are consistent with the observations of an increased columnar cell type in BE, the most consistent changes are associated with dysplasia, especially high-grade dypslasia (Table 2). These genes could serve as markers for progression in a clinical setting. For example, the number of genes which meet the described criteria for elevated expression in individual samples progressively increases through BE and dysplasia. The average of the number of markers detected per sample is 7.6 for BE, 11.7 for low-grade dysplasia, and 16.4 for high-grade dysplasia. Within the BE group, 3 samples have unusually high scores of 12, 12, and 14 markers detected. The two samples with 12 markers are different biopsies from the same patient: while the overall expression profiles vary between the 2 biopsies, they score identically in the marker analysis. Marker selection could be further refined to a subset associated with particular disease stages. This type of quantitative analysis may be of utility in identifying BE patients with greater risk of progression, and may be less sensitive to sampling and observer-related effects. Some of the secreted and processed factors listed (Table 1A, 2, 3) may even be detectable in the blood, which could further simplify screening.

Adenocarcinoma:

Many of the genes differentially expressed in adenocarcinoma in Barrett's, similar to other solid tumors, reflect the changes occurring as the cells acquire a more proliferative and invasive phenotype (Table 3). Included are genes involved with growth, cell adhesion, matrix invasion, vascularization, and intracellular remodeling. The majority of genes are most prevalent in adenocarinoma, but some are also detected at earlier stages. For example, genes likely to be involved in tumor angiogenesis showed significant upregulation in samples with dysplasia (eg. tumor endothelial marker 1 (TEM1), Tie2 ligand 2, VEGFC, endothelin 1).

TABLE 3 Genes up-regulated in esophageal adenocarcinoma

NCBI RefSeq	Gene families/genes	BE	D	BE-CA	CA
	Growth factors / receptors				
NM_005228	EGFR		(* H)		*
NM_004442	EPHB2				*
NM_003212	CRIPTO CR-1	(*)	*		*
NM_004429	Ephrin B1				* $
	Metalloproteinases - related				
NM_016155	MMP-17/ MT4-MMP				*
NM_021801	MMP26	(*)	(*)	(*)	* $
NM_001110	ADAM10			*	*
NM_001109	ADAM8		* H		(*)
XM_132370#	ADAM1		*		(*)
NM_003254	TIM1	*	*	*	*
	Intracellular cytoskeletal				
NM_001665	rho G	(*)		*	*
NM_006113	VAV3			*	*
NM_002086	GRB2		*	*	(*)
NM_001666	C1		* H		
NM_007124	Utrophin				*
	Transcription / nuclear				
NM_030756	Tcf4, DNA269446	(*)	*		*
NM_005252	c-Fos		*	*	*
NM_002592	PCNA			*	*
NM_004060	cyclin G		*		
NM_053056	Cyclin D1		*		(*) $
NM_003401	XRCC4				*
NM_007149	Zinc finger protein				*
	Cell surface adhesion / matrix				
XM_053256	MUC1	*	*	*	*
NM_004363	CEA		(*)		*
NM_002483	NCA				*

NM_006350	Follistatin		* H	(*)	* $
NM_021101	Claudin 1				* $
NM_012130	Claudin 14				*
NM_003285	tenascin-R	(*)	*		*
NM_001793	CAD3	(*)		*	*
NM_005076	AXO1		* H		
NM_001843	CONT		* H		
NM_000582	Osteopontin	(*)		*	*
NM_006499	Galectin 8	(*)			*
NM_001711	PGS1 (biglycan)	*	* L		
NM_001466	Frizzled 2				* $
NM_005545	ISLR				* $
NM_022763	FLJ23399	(*)		*	*
	Vascularization				
NM_020404	TEM1		* H		(*)
NM_001147	Tie2 ligand2		*	*	*
NM_003714	STC-2		* H		(*)
NM_005429	VEGFC		*		(*)
NM_000930	tPA			*	*
NM_001955	Endothelin 1		* H		(*)
NM_000361	Thrombomodulin			(*)	*
NM_001993	TF	(*)	*		*
	Channel / transmembrane				
NM_005282	GPR4			*	*
NM_006056	GPR66				*
NM_003058	SLC22A2	(*)	(* H)	*	*
NM_002420	MLSN1				*
NM_000702	ATN2, Na/K transport				*

Genes are associated with the disease states B3, dysplasia (D), BE adjacent to carcinoma (BE-CA), or carcinoma (CA) if present in at least 25% of samples tested. (*) indicates gene expression changes associated wiht 15-25% of samples.

$ indicates a target of the Wnt signalling pathway.

The gene expression profiles in Barrett's adenocarcinoma share many similarities with colon tumors. For example, epidermal growth factor receptor (EGFR; previously described in carcinoma in BE) (ak-Kasspooles et al., Internat. J. Cancer 54:213-219 (1993), along with other growth factor-related or cell-surface proteins such as Cripto CR1, EPHB2, MUC1, NCA/CEACAM6, CEA (Table 3), are often highly expressed in colon cancer (Ciardiello et al., Proc. Natl. Acad. Sci. USA 88:7792-7796 (1991); Liu et al., Cancer 94:934-939 (2002); Zimmerman et al., Proc. Natl. Acad. Sci. USA 84:2960-2964 (1987); Medina et al., Cancer Res. 59:1061-1070 (1999); and Ilantzis et al., Neoplasia 4:151-163 (2002)). The sodium channel associated with cystic fibrosis, CFTR, was upregulated in adenocarcinoma and can be detected in some cases of high-grade dysplasia (Table 2). This gene is also overexpressed in colon tumors. Furthermore, there is evidence that several genes listed are targets of Wnt signalling pathways (Table 3) (Tetsu and McCormick, Nature 398:422-426 (1999); Miwa et al., Oncol. Res. 12:469-476 (2000); Marchenko et al., Biochem. J. 363:253-262 (2002); Sagara et al., Biochem. and Biophys. Res. Comm. 252:117-122 (1998); Lescher et al., Dev. Dyn. 213:440-451 (1998); Willert et al., BMC Dev. Biol. 2:1-6 (2002); and Tice et al., J. Biol. Chem. 277:14329-14335 (2002)), and it is possible that COX-2, which is implicated in colon cancer as well as adenocarcinoma in Barrett's, is a Wnt pathway target (Howe et al., Cancer Res. 59:1572-1577 (1999)). An additional synergistic link is suggested by the recent finding that EGFR is activated by prostaglandin E2, a product of COX-2 (Tsujii et al., Cell 93:705-716 (1998); Tsujii et al., Proc. Natl. Acad. Sci. USA 94:3336-3340 (1997); and Pai et al., Nature Med. 8:289-293 (2002)).

More support for Wnt/beta catenin-like induction comes from the strong induction of transcription factor and TCF4 (TCF7L2) in several dysplasia and adenocarcinoma samples (Figure 3A). Knockout studies in mice indicate that TCF4 is necessary for the maintenance of proliferative crypts in the small intestine, and constitutive acitivity of TCF4 in APC-deficient human epithelial cells may contribute to their malignant transformation (Korinek et al., Nature Gen. 19:379-383 (1998)). Given its role in colon carcinogenesis, TCF4 provides another key link between intestinal metaplasia and carcinoma in BE.

Most genes listed represent known genes, but the novel gene FLJ23399 was one of the genes most consistently observed in adenocarcinoma and patient-matched adjacent BE samples (Figure 3B). Expression in BE adjacent to carcinoma suggests the induction may be epigenetic, or possibly reflect small foci of adencarcinoma that cannot be identified

histologically. Increased expression of this gene was also discovered herein to be associated with colon tumors, and with metastatic prostate tumors (increased expression with metastasis as compared to primary tumors). Its function is unknown, but the presence of 4 type III fibronectin domains in the putative extracellular region suggest a possible role in cell adhesion and/or cell-matrix interactions.

Barrett's Esophagus-to-Adenocarcinoma Disease Progression:

Despite the difficulties associated with sampling and interpretation, the presence and degree of dysplasia is still the most predictive factor for risk of progression to adenocarinoma (Miros et al., Gut 32:1441-1446 (1991)). Foci of carcinoma typically appear adjacent to dysplasia, and esophageal resections of high-grade dysplasia frequently contain previously unrecognized adenocarcinoma (Falk et al., Gastrointest. Endosc. 49:170-176 (1999); and Cameron and Carpenter, Am. J. Gastroenterol. 92:586-591 (1997)). In this study, by the time dysplasia was apparent, there was evidence of progressive development toward a gene expression profile similar to a differentiated small intestinal enterocyte (along with a small group of genes representative of other intestinal cell types). A possible key contributing factor is the increased expression of TCF4 with advancing disease. Homozygous disruption of TCF4 in mice results in death shortly after birth, and the neonatal epithelium is composed only of non-dividing villus cells (Korinek, V. et al., Nature Gen. 19:379-383 (1998)). This suggests that the genetic program controlled by TCF4 maintains, and possibly establishes, the crypt stem cells of the small intestine. In humans, TCF4 is expressed strongly in the crypts in early fetal development, with increasing expression on the villi up to week 22 as the small intestine develops (Barker et al., Am. J. Pathol. 154:29-35 (1999)). TCF4 is also expressed along the crypt-villus axis of adult small intestine and along the epithelial lining of the crypts of adult colon. The TCF4 profile observed in dysplasia and carcinoma in BE may reflect the inappropriate activation of a developmental pathway with a possible underlying dynamic and differentiating stem cell-like population, or acquisition of some of these characteristics. The delicate cells of the small intestine, with their specialized absorptive and digestive functions and rapid turnover, would seem highly susceptible to damage in the context of the esophagus and gastrointestinal reflux disease.

The developing intestinal phenotype apparent by progression to dysplasia, associated with increased expression of TCF4, suggests some tantalizing links to the development of

carcinoma and the similarities in gene expression between adenocarcinoma of the esophagus and colon. In the context of loss of APC function, association of beta catenin with TCF4 results in constitutive transcription of Tcf target genes, a proposed crucial event in the early transformation of colonic epithelia in colon cancer (Korinek et al., Science 275:1784-1787 (1997)). While there is not strong evidence of truncating mutations in APC or oncogenic beta catenin in esophageal adenocarcinoma, there is evidence of hypermethylation of the APC promoter (in 48/52 of adenocarcinoma patients and 17/43 patients with BE metaplasia) (Kawakami et al., J. Natl. Cancer Inst. 92:1805-1811 (2000)). APC hypermethylation has also been implicated in progression in colon cancer (Hiltunen et al., Int. J. Cancer 70:644-648 (1997)). In this context, it is interesting to note that elevated c-Fos expression was apparent in our study in both dysplasia and carcinoma (Table 3). This could perhaps be related to the presence of bile acids from reflux, overexpression of proglucagon-derived peptide GLP2 (Table 2), or of TNFa (Table 1), all of which have been shown to induce c-Fos expression (Bakin and Curran, Science 283:387-390 (1999); Di Toro et al., Eur. J. Pharm. Sci. 11:291-298 (2000); and Bjerknes and Cheng, Proc. Natl. Acad. Sci. USA 98:12497-12502 (2001)). One proposal for oncogenic transformation by c-Fos is hypermethylation resulting from induction of DNA 5-methylcytosine transferase (Goetze et al., Atherosclerosis 159:93-101 (2001)). These factors may contribute to a potential increased availability of beta catenin to combine with TCF4 and activate transcriptional pathways that contribute to carcinogenesis. c-Fos may play an earlier role in intestinal metaplasia as well: studies of intestinal development in mice indicate that GLP2-mediated induction of c-Fos in enteric neurons signals growth of columnar epithelial cell progenitors and stem cells (Di Toro et al., Eur. J. Pharm. Sci. 11:291-298 (2000)).

Gene expression profiling of esophageal biopsies has revealed several intriguing associations for the progression of malignancy in the context of Barrett's esophagus. Many of the genes may be involved in potentiating regulatory cycles, and there is potential synergy for the development of adenocarcinoma between exposure to damaging agents (eg. bile), inflammatory response and prostaglandin synthesis, intestinal metaplasia and TCF4 induction, along with induction of growth factors such as EGFR and oncogenes such as c-Fos. Subsets of the genes identified may also eventually serve as markers to identify patients at higher risk for adenocarcinoma. This could permit streamlining of expensive and time-consuming surveillance programs, along with earlier detection and associated improved survival chances for high-risk patients.

Diagnosis of High-grade Esophageal Dysplasia and Prognosis of Esophageal Adenocarcinoma:

Several HGD gene markers were discovered as being up-regulated at least 1.5-fold in many high-grade dysplasia samples but are up-regulated in relatively few Barrett's esophagus samples (see Table 4A compared to Table 4B). According to the invention, where at least eight of the twenty-two HGD gene markers are detected to be up-regulated at 1.5-fold in an esophageal tissue sample, cells of the tissue sample are said to exhibit HGD. In addition, the patient from whom the sample was taken may be diagnosed as experiencing high-grade esophageal dysplasia. Further, the prognosis for the patient includes the likely development of adenocarcinoma. Based on the detection of HGD, diagnosis and prognosis, the patient may be treated accordingly and at an earlier stage in the BE-to-cancer progression than would otherwise have occurred prior to disclosure of the instant invention. Alternatively, in a test esophageal tissue sample, where at least one of the at least eight up-regulated HGD marker genes is AGR2 (SEQ ID NO:3), TM7SF1 (SEQ ID NO:13), MAT2B (SEQ ID NO:17), SLNAC1 (SEQ ID NO:23), or TCF4 (SEQ ID NO:43), cells of the tissue sample exhibit HGD and the the patient is said to be diagnosed as experiencing dysplasia, particularly high-grade dysplasia, and is likely to develop adenocarcinoma.

Table 4A High-grade Dysplasia Markers

							Sample ID #			
NCBI #	SEQ ID NO: (na and aa)	Gene name		2493	2955	2491	Z score* 2958	3128	2493	3130
NM_001955	1 and 2	Endothelin 1	ET-1	2.9		1.9	2.7	2.2		
NM_006408	3 and 4	anterior gradient 2 (Xenepus laevis) homolog	AGR2	3.1	2.7	2.6	2.7	3.4	2.	2.9
NM_001109	5 and 6	ADAM8	ADAM8	3.6		1.8		2.3		
NM_002773	7 and 8	Prostasin precursor, serine protease	PRSS8	2.5	1.8	2.7		3.1	2.3	
NM_005076	9 and 10	Axonin-1 precursor	AXO1	2.		1.6	2.		1.5	
NM_021969	11 and 12	Nuclear hormone receptor	NROB2	4.9		2.1	2.8	3.6	2.6	2.7
NM_003272	13 and 14	TM7SF1	TM7SF1	1.5	3.6	2.3	1.7	3.	2.2	1.7
NM_000108	15 and 16	dihydrolipamide dehydrogenase	DLDH	2.1	3.2	1.9	1.7			
NM_013283	17 and 18	methionine adenosyltransferase II, beta	MAT2B	2.5	1.8	2.2	3.	2.7		
NM_003714	19 and 20	stanniocalcin-2	STC-2	2.3		1.7	1.9	1.6		1.9
NM_001631	21 and 22	Alkaline phosphatase, intestinal precursor	PPBI	2.3		1.6	2.	2.4	ND	
NM_004769	23 and 24	Sodium channel receptor SLNAC1	SLNAC1	2.9	1.8	3.6	3.	2.9	ND	2.5
NM_000717	25 and 26	Carbonic anhydrase iv precursor	CAH4				1.7	1.8		1.8
NM_000928	27 and 28	Phospholipase a2 precursor	PA21	2.				2.4	2.4	
NM_005242	29 and 30	Proteinase activated receptor 2 precursor	PAR2				2.9		2.7	
NM_004969	31 and 32	Insulin-degrading enzyme	IDE		1.6	2.5	4.4	1.8	1.9	1.8
NM_005379	33 and 34	Myosin IA (MYO1A)	MYO1A		1.8	2.3	1.5			

NM_000775	35 and 36	Cytochrome P450 monooxygenase CYP2J2	CYP2J2		2.4		4.3	2.3		
NM_006214	37 and 38	Phytanoyl-CoA hydroxylase (Refsum disease)	PHYH		2.9		2.4		1.9	
NM_001914	39 and 40	"Cytochrome b5 , 3' end"	CYB5			3.			2.4	
NM_001863	41 and 42	"CoxVIb gene, last exon and flanking sequence"	coxVIb	1.9		2.2	2.	1.9		1.6
NM_030756	43 and 44	TCF4	TCF4	3.6		2.6	6.8	3.5	4.1	
		total number		15	10	17	18	16	12	8

Z score cut-off was 1.5 or above ($p < 0.07$). "na" and "aa" refer to the nucleic acid and amino acid SEQ ID NO, respectively, for the associated markers.

Table 4B Low Prevalence of HGD Markers

NCBI #	SEQ ID NO: (na and aa)	Gene name	Sample ID #																
			Z score*																
			B-15	B-17	B-18	B	3091	3131	3132	3142	3143	3088	2296	2554	2555	3134	3135	3140	3181	3141
NM_001955	1 and 2	ET-1																		
NM_006408	3 and 4	AGR2				2.5													1.5	
NM_001109	5 and 6	ADAM8		2.2																
NM_002773	7 and 8	PRSS8			3.4	1.5														
NM_005076	9 and 10	AXO1																		
NM_021969	11 and 12	NROB2			3.2			2.4	2.4	2.2		1.7		1.7	2.6	1.5				
NM_003272	13 and 14	TM7SF1			3.1															
NM_000108	15 and 16	DLDH	2.																	
NM_013283	17 and 18	MAT2B				2.4														
NM_003714	19 and 20	STC-2																		
NM_001631	21 and 22	PPBI						2.												
NM_004769	23 and 24	SLNAC1	2.8																	
NM_000717	25 and 26	CAH4		1.8	1.5															1.5
NM_000928	27 and 28	PA21									4.2	4.7		2.6	4.3				7.4	
NM_005242	29 and 30	PAR2																		
NM_004969	31 and 32	IDE				1.5									2.6				2.8	4.9

NM_005379	33 and 34	MYO1A	1.5						1.6	1.6		1.7						1.6		
NM_000775	35 adn 36	CYP2J2														5.7				
NM_006214	37 and 38	PHYH											1.6						3.2	
NM_001914	39 and 40	CYB5	5.3	1.8																
NM_001863	41 and 42	coxVIb	1.8	1.9								1.7				2.1				
NM_030756	43 and 44	TCF4			2.4													2.3		
		Total #	5	4	5	4	0	2	2	2	1	4	1	2	3	3	0	2	4	2

Z score cut-off was 1.5 or above ($p < 0.07$). "na" and "aa" refer to the nucleic acid and amino acid SEQ ID NO, respectively, for the associated markers.

In addition to detecting and diagnosing HGD and developing a prognosis of esophageal adenocarcinoma, treatment of cancer, including, but not limited to adenocarcinoma, esophageal adenocarcioma, and colon cancer is also possible by administering to a patient a therapeutically effective amount of an antagonist of one or more of the following adenocarcinoma marker polypeptides: CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:46), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:48), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:24), CFTR (chloride channel, NM_000492) (SEQ ID NO:50), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:52), PRSS8 (serine protease, NM_002773) (SEQ ID NO:8), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:28), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:4), EGFR (NM_005228) (SEQ ID NO:54), EPHB2 (NM_004442) (SEQ ID NO:56), CRIPTO CR-1 (NM_003212) (SEQ ID NO:58), Eprin B1 (NM_004429) (SEQ ID NO:60), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:62), MMP26 (NM_021801) (SEQ ID NO:64), ADAM10 (NM_001110) (SEQ ID NO:66), ADAM8 (NM_001109) (SEQ ID NO:6), ADAM1 (XM_132370) (SEQ ID NO:68), TIM1 (NM_003254) (SEQ ID NO:70), MUC1 (XM_053256) (SEQ ID NO:72), CEA (NM_004363) (SEQ ID NO:74), NCA (NM_002483) (SEQ ID NO:76), Follistatin (NM_006350) (SEQ ID NO:78), Claudin 1 (NM_021101) (SEQ ID NO:80), Claudin 14 (NM_012130) (SEQ ID NO:82), tenascin-R (NM_003285) (SEQ ID NO:84), CAD3 (NM_001793) (SEQ ID NO:86), AXO1 (NM_005076) (SEQ ID NO:10), CONT (NM_001843) (SEQ ID NO:88), Osteopontin (NM_000582) (SEQ ID NO:90), Galectin 8 (NM_006499) (SEQ ID NO:92), PGS1 (bihlycan, NM_001711) (SEQ ID NO:94), Frizzled 2 (NM_001466) (SEQ ID NO:96), ISLR (NM_005545) (SEQ ID NO:98), FLJ23399 (NM_022763) (SEQ ID NO:100), TEM1 (NM_020404) (SEQ ID NO:102), Tie2 ligand2 (NM_001147) (SEQ ID NO:104), STC-2 (NM_003714) (SEQ ID NO:20), VEGFC (NM_005429) (SEQ ID NO:106), tPA (NM_000930) (SEQ ID NO:108), Endothelin 1 (NM_001955) (SEQ ID NO:2), Thrombomodulin (NM_000361) (SEQ ID NO:110), TF (NM_001993) (SEQ ID NO:112), GPR4 (NM_005282) (SEQ ID NO:114), GPR66 (NM_006056) (SEQ ID NO:116), SLC22A2 (NM_003058) ((SEQ ID NO:118), MLSN1 (NM_002420) (SEQ ID NO:120), or ATN2 (Na/K transport, NM_000702) (SEQ ID NO:122). The antagonist is a small molecule that binds and inactivates the polypeptide; binds and inactivates a precursor of the polypeptide; prevents translation of the polypeptide; prevents its transcription; or the like. Alternatively, the antagonist is an antibody that specifically binds the polypeptide and inhibits or prevents its activity. Where the antagonist is an antibody, the antibody is optionally a monoclonal antibody, a humanized antibody, or a binding fragment

thereof. The treatment involves contacting a cancer cell with an antagonist of at least one of the polypeptides encoded by the adenocarcinoma marker genes listed above, alternatively with an antagonist of at least three, alternatively with at least five, and alternatively with at least eight of the polypeptides encoded by the adenocarcinoma marker genes listed above.

Further, a method of screening for a compound that inhibits cancer cell growth or causes the death of a cancer cell, particularly an adenocarcinoma cell, an esophageal adenocarcinoma cell, or a colon cancer cell, is an aspect of the invention. Accordingly, the screening method involves contacting a cancer cell, such as one expressing at least one, three, five, eight or more of the adenocarcinoma gene markers selected from the group consisiting of CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:45), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:47), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:23), CFTR (chloride channel, NM_000492) (SEQ ID NO:49), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:51), PRSS8 (serine protease, NM_002773) (SEQ ID NO:7), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:27), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:3), EGFR (NM_005228) (SEQ ID NO:53), EPHB2 (NM_004442) (SEQ ID NO:55), CRIPTO CR-1 (NM_003212) (SEQ ID NO:57), Eprin B1 (NM_004429) (SEQ ID NO:59), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:61), MMP26 (NM_021801) (SEQ ID NO:63), ADAM10 (NM_001110) (SEQ ID NO:65), ADAM8 (NM_001109) (SEQ ID NO:5), ADAM1 (XM_132370) (SEQ ID NO:67), TIM1 (NM_003254) (SEQ ID NO:69), MUC1 (XM_053256) (SEQ ID NO:71), CEA (NM_004363) (SEQ ID NO:73), NCA (NM_002483) (SEQ ID NO:75), Follistatin (NM_006350) (SEQ ID NO:77), Claudin 1 (NM_021101) (SEQ ID NO:79), Claudin 14 (NM_012130) (SEQ ID NO:81), tenascin-R (NM_003285) (SEQ ID NO:83), CAD3 (NM_001793) (SEQ ID NO:85), AXO1 (NM_005076) (SEQ ID NO:9), CONT (NM_001843) (SEQ ID NO:87), Osteopontin (NM_000582) (SEQ ID NO:89), Galectin 8 (NM_006499) (SEQ ID NO:91), PGS1 (bihlycan, NM_001711) (SEQ ID NO:93), Frizzled 2 (NM_001466) (SEQ ID NO:95), ISLR (NM_005545) (SEQ ID NO:97), FLJ23399 (NM_022763) (SEQ ID NO:99), TEM1 (NM_020404) (SEQ ID NO:101), Tie2 ligand2 (NM_001147) (SEQ ID NO:103), STC-2 (NM_003714) (SEQ ID NO:19), VEGFC (NM_005429) (SEQ ID NO:105), tPA (NM_000930) (SEQ ID NO:107), Endothelin 1 (NM_001955) (SEQ ID NO:1), Thrombomodulin (NM_000361) (SEQ ID NO:109), TF (NM_001993) (SEQ ID NO:111), GPR4 (NM_005282) (SEQ ID NO:113), GPR66 (NM_006056) (SEQ ID NO:115), SLC22A2 (NM_003058) ((SEQ ID NO:117), MLSN1 (NM_002420) (SEQ ID NO:119), and ATN2

(Na/K transport, NM_000702) (SEQ ID NO:121), followed by determining cancer cell growth inhibition or cancer cell death.

Example 5: Nucleic acid and amino acid sequence identity determinations:

As shown below, Table 5 provides the complete source code for the ALIGN-2 sequence comparison computer program. This source code may be routinely compiled for use on a UNIX operating system to provide the ALIGN-2 sequence comparison computer program.

In addition, disclosed herein are hypothetical exemplifications for using the below described method to determine % amino acid sequence identity and % nucleic acid sequence identity using the ALIGN-2 sequence comparison computer program, wherein "PRO" represents the amino acid sequence of a hypothetical HGD marker polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, "PRO-DNA" represents a hypothetical HGD marker polypeptide-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, "X", "Y", and "Z" each represent different hypothetical amino acid residues and "N", "L" and "V" each represent different hypothetical nucleotides.

Table 5

```
/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define      _M    -8     /* value of a match with a stop */

int     _day[26][26] = {
/*      A B C D E F G H I J K L M N O P Q R S T U V W X Y Z*/
```

```
/* A */  { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */  { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */  {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4,_M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */  { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */  { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
/* F */  {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4,_M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */  { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0,_M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */  {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2,_M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */  {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2,_M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */  {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1,_M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */  {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */  {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2,_M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */  { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2,_M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */  {_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,
0,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M},
/* P */  { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */  { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1,_M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */  {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0,_M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */  { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1,_M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
/* T */  { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0,_M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */  { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2,_M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */  {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4,_M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */  {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2,_M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */  { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1,_M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};
```

Page 1 of day.h

```
/*
 */
#include <stdio.h>
#include <ctype.h>

#define     MAXJMP    16    /* max jumps in a diag */
#define     MAXGAP    24    /* don't continue to penalize gaps larger than this */
#define     JMPS      1024  /* max jmps in an path */
#define     MX        4     /* save if there's at least MX-1 bases since last jmp */

#define     DMAT      3     /* value of matching bases */
#define     DMIS      0     /* penalty for mismatched bases */
#define     DINS0     8     /* penalty for a gap */
#define     DINS1     1     /* penalty per base */
#define     PINS0     8     /* penalty for a gap */
#define     PINS1     4     /* penalty per residue */

struct jmp {
        short           n[MAXJMP]; /* size of jmp (neg for dely) */
        unsigned short  x[MAXJMP]; /* base no. of jmp in seq x */
};                                 /* limits seq to 2^16 -1 */

struct diag {
        int             score;     /* score at last jmp */
```

```
        long        offset;     /* offset of prev block */
        short       ijmp;       /* current jmp index */
        struct jmp  jp;         /* list of jmps */
};

struct path {
        int     spc;        /* number of leading spaces */
        short   n[JMPS];    /* size of jmp (gap) */
        int     x[JMPS];    /* loc of jmp (last elem before gap) */
};

char        *ofile;         /* output file name */
char        *namex[2];      /* seq names: getseqs() */
char        *prog;          /* prog name for err msgs */
char        *seqx[2];               /* seqs: getseqs() */
int         dmax;           /* best diag: nw() */
int         dmax0;          /* final diag */
int         dna;            /* set if dna: main() */
int         endgaps;                /* set if penalizing end gaps */
int         gapx, gapy;     /* total gaps in seqs */
int         len0, len1;     /* seq lens */
int         ngapx, ngapy;   /* total size of gaps */
int         smax;           /* max score: nw() */
int         *xbm;           /* bitmap for matching */
long        offset;         /* current offset in jmp file */
struct diag *dx;            /* holds diagonals */
struct path pp[2];          /* holds path for seqs */

char        *calloc(), *malloc(), *index(), *strcpy();
char        *getseq(), *g_calloc();
```

```
/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *  where file1 and file2 are two dna or two protein sequences.
 *  The sequences can be in upper- or lower-case an may contain ambiguity
 *  Any lines beginning with ';', '>' or '<' are ignored
 *  Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *  A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *  Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static  _dbval[26] = {
        1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static  _pbval[26] = {
        1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
        128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
        1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
        1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                                    main
        int     ac;
        char    *av[];
{
        prog = av[0];
        if (ac != 3) {
```

```
        fprintf(stderr,"usage: %s file1 file2\n", prog);
        fprintf(stderr,"where file1 and file2 are two dna or two protein sequences.\n");
        fprintf(stderr,"The sequences can be in upper- or lower-case\n");
        fprintf(stderr,"Any lines beginning with ';' or '<' are ignored\n");
        fprintf(stderr,"Output is in the file \"align.out\"\n");
        exit(1);
    }
    namex[0] = av[1];
    namex[1] = av[2];
    seqx[0] = getseq(namex[0], &len0);
    seqx[1] = getseq(namex[1], &len1);
    xbm = (dna)? _dbval : _pbval;

    endgaps = 0;            /* 1 to penalize endgaps */
    ofile = "align.out";    /* output file */

    nw();       /* fill in the matrix, get the possible jmps */
    readjmps(); /* get the actual jmps */
    print();    /* print stats, alignment */

    cleanup(0); /* unlink any tmp files */
}
```

```
/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw()                                                              nw
{
        char    *px, *py;               /* seqs and ptrs */
        int     *ndely, *dely; /* keep track of dely */
        int     ndelx, delx;    /* keep track of delx */
        int     *tmp;           /* for swapping row0, row1 */
        int     mis;            /* score for each type */
        int     ins0, ins1;     /* insertion penalties */
        register        id;             /* diagonal index */
        register        ij;             /* jmp index */
        register        *col0, *col1;   /* score for curr, last row */
        register        xx, yy;         /* index into seqs */

        dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

        ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
        dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
        col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
        col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
        ins0 = (dna)? DINS0 : PINS0;
        ins1 = (dna)? DINS1 : PINS1;

        smax = -10000;
        if (endgaps) {
                for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
                        col0[yy] = dely[yy] = col0[yy-1] - ins1;
```

```
                ndely[yy] = yy;
            }
            col0[0] = 0;    /* Waterman Bull Math Biol 84 */
        }
        else
            for (yy = 1; yy <= len1; yy++)
                dely[yy] = -ins0;

        /* fill in match matrix
         */
        for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
            /* initialize first entry in col
             */
            if (endgaps) {
                if (xx == 1)
                    col1[0] = delx = -(ins0+ins1);
                else
                    col1[0] = delx = col0[0] - ins1;
                ndelx = xx;
            }
            else {
                col1[0] = 0;
                delx = -ins0;
                ndelx = 0;
            }
```

...nw

```
for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
                mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
                mis += _day[*px-'A'][*py-'A'];

        /* update penalty for del in x seq;
         * favor new del over ongong del
         * ignore MAXGAP if weighting endgaps
         */
        if (endgaps || ndely[yy] < MAXGAP) {
                if (col0[yy] - ins0 >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else {
                        dely[yy] -= ins1;
                        ndely[yy]++;
                }
        } else {
                if (col0[yy] - (ins0+ins1) >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else
                        ndely[yy]++;
        }

        /* update penalty for del in y seq;
         * favor new del over ongong del
         */
        if (endgaps || ndelx < MAXGAP) {
                if (col1[yy-1] - ins0 >= delx) {
```

```
                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
            } else {
                delx -= ins1;
                ndelx++;
            }
        } else {
            if (col1[yy-1] - (ins0+ins1) >= delx) {
                delx = col1[yy-1] - (ins0+ins1);
                ndelx = 1;
            } else
                ndelx++;
        }

        /* pick the maximum score; we're favoring
         * mis over any del and delx over dely
         */
```

...nw

```
                id = xx - yy + len1 - 1;
                if (mis >= delx && mis >= dely[yy])
                        col1[yy] = mis;
                else if (delx >= dely[yy]) {
                        col1[yy] = delx;
                        ij = dx[id].ijmp;
                        if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
                        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                                dx[id].ijmp++;
                                if (++ij >= MAXJMP) {
                                        writejmps(id);
                                        ij = dx[id].ijmp = 0;
                                        dx[id].offset = offset;
                                        offset += sizeof(struct jmp) + sizeof(offset);
                                }
                        }
                        dx[id].jp.n[ij] = ndelx;
                        dx[id].jp.x[ij] = xx;
                        dx[id].score = delx;
                }
                else {
                        col1[yy] = dely[yy];
                        ij = dx[id].ijmp;

        if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
                        && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                                dx[id].ijmp++;
                                if (++ij >= MAXJMP) {
                                        writejmps(id);
                                        ij = dx[id].ijmp = 0;
                                        dx[id].offset = offset;
                                        offset += sizeof(struct jmp) + sizeof(offset);
                                }
```

```
                        }
                        dx[id].jp.n[ij] = -ndely[yy];
                        dx[id].jp.x[ij] = xx;
                        dx[id].score = dely[yy];
                }
                if (xx == len0 && yy < len1) {
                        /* last col
                         */
                        if (endgaps)
                                col1[yy] -= ins0+ins1*(len1-yy);
                        if (col1[yy] > smax) {
                                smax = col1[yy];
                                dmax = id;
                        }
                }
        }
        if (endgaps && xx < len0)
                col1[yy-1] -= ins0+ins1*(len0-xx);
        if (col1[yy-1] > smax) {
                smax = col1[yy-1];
                dmax = id;
        }
        tmp = col0; col0 = col1; col1 = tmp;
    }
    (void) free((char *)ndely);
    (void) free((char *)dely);
    (void) free((char *)col0);
    (void) free((char *)col1);
}
```

```
/*
 *
 * print() -- only routine visible outside this module
 *
 * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align() -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align()
 * nums() -- put out a number line: dumpblock()
 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() - -put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC   3
#define P_LINE      256     /* maximum output line */
#define P_SPC       3       /* space between name or num and seq */

extern _day[26][26];
int     olen;           /* set output line length */
FILE    *fx;            /* output file */

print()                                                          print
{
        int     lx, ly, firstgap, lastgap;          /* overlap */

        if ((fx = fopen(ofile, "w")) == 0) {
                fprintf(stderr,"%s: can't write %s\n", prog, ofile);
                cleanup(1);
        }
        fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
```

```
        fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
        olen = 60;
        lx = len0;
        ly = len1;
        firstgap = lastgap = 0;
        if (dmax < len1 - 1) {  /* leading gap in x */
                pp[0].spc = firstgap = len1 - dmax - 1;
                ly -= pp[0].spc;
        }
        else if (dmax > len1 - 1) {      /* leading gap in y */
                pp[1].spc = firstgap = dmax - (len1 - 1);
                lx -= pp[1].spc;
        }
        if (dmax0 < len0 - 1) {          /* trailing gap in x */
                lastgap = len0 - dmax0 -1;
                lx -= lastgap;
        }
        else if (dmax0 > len0 - 1) {     /* trailing gap in y */
                lastgap = dmax0 - (len0 - 1);
                ly -= lastgap;
        }
        getmat(lx, ly, firstgap, lastgap);
        pr_align();
}
```

```
/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)                                    getmat
        int     lx, ly;                 /* "core" (minus endgaps) */
        int     firstgap, lastgap;              /* leading trailing overlap */
{
        int             nm, i0, i1, siz0, siz1;
        char            outx[32];
        double          pct;
        register                n0, n1;
        register char   *p0, *p1;

        /* get total matches, score
         */
        i0 = i1 = siz0 = siz1 = 0;
        p0 = seqx[0] + pp[1].spc;
        p1 = seqx[1] + pp[0].spc;
        n0 = pp[1].spc + 1;
        n1 = pp[0].spc + 1;

        nm = 0;
        while ( *p0 && *p1 ) {
                if (siz0) {
                        p1++;
                        n1++;
                        siz0--;
                }
                else if (siz1) {
                        p0++;
                        n0++;
                        siz1--;
```

```
            }
            else {
                if (xbm[*p0-'A']&xbm[*p1-'A'])
                    nm++;
                if (n0++ == pp[0].x[i0])
                    siz0 = pp[0].n[i0++];
                if (n1++ == pp[1].x[i1])
                    siz1 = pp[1].n[i1++];
                p0++;
                p1++;
            }
        }

        /* pct homology:
         * if penalizing endgaps, base is the shorter seq
         * else, knock off overhangs and take shorter core
         */
        if (endgaps)
            lx = (len0 < len1)? len0 : len1;
        else
            lx = (lx < ly)? lx : ly;
        pct = 100.*(double)nm/(double)lx;
        fprintf(fx, "\n");
        fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
            nm, (nm == 1)? "" : "es", lx, pct);
```

```
        fprintf(fx, "<gaps in first sequence: %d", gapx);                    ...getmat
        if (gapx) {
                (void) sprintf(outx, " (%d %s%s)",
                        ngapx, (dna)? "base":"residue", (ngapx == 1)? "":"s");
                fprintf(fx,"%s", outx);

        fprintf(fx, ", gaps in second sequence: %d", gapy);
        if (gapy) {
                (void) sprintf(outx, " (%d %s%s)",
                        ngapy, (dna)? "base":"residue", (ngapy == 1)? "":"s");
                fprintf(fx,"%s", outx);
        }
        if (dna)
                fprintf(fx,
                "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per
base)\n",
                smax, DMAT, DMIS, DINS0, DINS1);
        else
                fprintf(fx,
                "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per
residue)\n",
                smax, PINS0, PINS1);
        if (endgaps)
                fprintf(fx,
                "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
                firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
                lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
        else
                fprintf(fx, "<endgaps not penalized\n");
}

static          nm;             /* matches in core -- for checking */
static          lmax;           /* lengths of stripped file names */
```

```
static          ij[2];          /* jmp index for a path */
static          nc[2];          /* number at start of current line */
static          ni[2];          /* current elem number -- for gapping */
static          siz[2];
static char     *ps[2];         /* ptr to current element */
static char     *po[2];         /* ptr to next output char slot */
static char     out[2][P_LINE];     /* output line */
static char     star[P_LINE]; /* set by stars() */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align()                                                    pr_align
{
        int             nn;     /* char count */
        int             more;
        register                i;

        for (i =  0, lmax = 0; i < 2; i++) {
                nn = stripname(namex[i]);
                if (nn > lmax)
                        lmax = nn;

                nc[i] = 1;
                ni[i] = 1;
                siz[i] = ij[i] = 0;
                ps[i] = seqx[i];
                po[i] = out[i];
        }
```

```
for (nn = nm = 0, more = 1; more; ) {
        for (i = more = 0; i < 2; i++) {
                /*
                 * do we have more of this sequence?
                 */
                if (!*ps[i])
                        continue;

                more++;

                if (pp[i].spc) { /* leading space */
                        *po[i]++ = ' ';
                        pp[i].spc--;
                }
                else if (siz[i]) {          /* in a gap */
                        *po[i]++ = '-';
                        siz[i]--;
                }
                else {              /* we're putting a seq element
                                     */
                        *po[i] = *ps[i];
                        if (islower(*ps[i]))
                                *ps[i] = toupper(*ps[i]);
                        po[i]++;
                        ps[i]++;

                        /*
                         * are we at next gap for this seq?
                         */
                        if (ni[i] == pp[i].x[ij[i]]) {
                                /*
                                 * we need to merge all gaps
                                 * at this location
```

```
                                        */
                                        siz[i] = pp[i].n[ij[i]++];
                                        while (ni[i] == pp[i].x[ij[i]])
                                                siz[i] += pp[i].n[ij[i]++];
                                }
                                ni[i]++;
                        }
                }
                if (++nn == olen || !more && nn) {
                        dumpblock();
                        for (i = 0; i < 2; i++)
                                po[i] = out[i];
                        nn = 0;
                }
        }
}

/*
 * dump a block of lines, including numbers, stars: pr_align()
 */
static
dumpblock()                                                     dumpblock
{
        register        i;

        for (i = 0; i < 2; i++)
                *po[i]-- = '\0';
```

...dumpblock

```
        (void) putc('\n', fx);
        for (i = 0; i < 2; i++) {
                if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
                        if (i == 0)
                                nums(i);
                        if (i == 0 && *out[1])
                                stars();
                        putline(i);
                        if (i == 0 && *out[1])
                                fprintf(fx, star);
                        if (i == 1)
                                nums(i);
                }
        }
}

/*
 * put out a number line: dumpblock()
 */
static
nums(ix)                                                        nums
        int     ix;     /* index in out[] holding seq line */
{
        char            nline[P_LINE];
        register                i, j;
        register char  *pn, *px, *py;

        for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
                *pn = ' ';
        for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
                if (*py == ' ' || *py == '-')
```

```
                *pn = ' ';
            else {
                if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                    j = (i < 0)? -i : i;
                    for (px = pn; j; j /= 10, px--)
                        *px = j%10 + '0';
                    if (i < 0)
                        *px = '-';
                }
                else
                    *pn = ' ';
                i++;
            }
        }
        *pn = '\0';
        nc[ix] = i;
        for (pn = nline; *pn; pn++)
            (void) putc(*pn, fx);
        (void) putc('\n', fx);
}

/*
 * put out a line (name, [num], seq, [num]): dumpblock()
 */
static
putline(ix)                                                    putline
        int     ix;
{
```

...putline

```
        int             i;
        register char  *px;

        for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
                (void) putc(*px, fx);
        for (; i < lmax+P_SPC; i++)
                (void) putc(' ', fx);

        /* these count from 1:
         * ni[] is current element (from 1)
         * nc[] is number at start of current line
         */
        for (px = out[ix]; *px; px++)
                (void) putc(*px&0x7F, fx);
        (void) putc('\n', fx);
}

/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock()
 */
static
stars()                                                          stars
{
        int             i;
        register char  *p0, *p1, cx, *px;

        if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
           !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
                return;
        px = star;
```

```
        for (i = lmax+P_SPC; i; i--)
                *px++ = ' ';

        for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
                if (isalpha(*p0) && isalpha(*p1)) {

                        if (xbm[*p0-'A']&xbm[*p1-'A']) {
                                cx = '*';
                                nm++;
                        }
                        else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                                cx = '.';
                        else
                                cx = ' ';
                }
                else
                        cx = ' ';
                *px++ = cx;
        }
        *px++ = '\n';
        *px = '\0';
}
```

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
stripname(pn)                                                    stripname
        char    *pn;    /* file name (may be path) */
{
        register char  *px, *py;

        py = 0;
        for (px = pn; *px; px++)
                if (*px == '/')
                        py = px + 1;
        if (py)
                (void) strcpy(pn, py);
        return(strlen(pn));

}
```

```
/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_calloc() -- calloc() with error checkin
 * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";             /* tmp file for jmps */
FILE    *fj;

int     cleanup();                              /* cleanup tmp file */
long    lseek();

/*
 * remove any tmp file if we blow
 */
cleanup(i)                                                          cleanup
        int     i;
{
        if (fj)
                (void) unlink(jname);
        exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
```

```
getseq(file, len)                                                    getseq
        char    *file;  /* file name */
        int     *len;   /* seq len */
{
        char            line[1024], *pseq;
        register char   *px, *py;
        int             natgc, tlen;
        FILE            *fp;

        if ((fp = fopen(file,"r")) == 0) {
                fprintf(stderr,"%s: can't read %s\n", prog, file);
                exit(1);
        }
        tlen = natgc = 0;
        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++)
                        if (isupper(*px) || islower(*px))
                                tlen++;
        }
        if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                fprintf(stderr,"%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
                exit(1);
        }
        pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
```

...getseq

```
        py = pseq + 4;
        *len = tlen;
        rewind(fp);

        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++) {
                        if (isupper(*px))
                                *py++ = *px;
                        else if (islower(*px))
                                *py++ = toupper(*px);
                        if (index("ATGCU",*(py-1)))
                                natgc++;
                }
        }
        *py++ = '\0';
        *py = '\0';
        (void) fclose(fp);
        dna = natgc > (tlen/3);
        return(pseq+4);
}

char    *
g_calloc(msg, nx, sz)                                   g_calloc
        char    *msg;           /* program, calling routine */
        int     nx, sz;         /* number and size of elements */
{
        char            *px, *calloc();

        if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
                if (*msg) {
```

```
                fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg,
nx, sz);
                exit(1);
            }
        }
        return(px);
}

/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
 */
readjmps()                                                    readjmps
{
        int         fd = -1;
        int         siz, i0, i1;
        register    i, j, xx;

        if (fj) {
            (void) fclose(fj);
            if ((fd = open(jname, O_RDONLY, 0)) < 0) {
                fprintf(stderr, "%s: can't open() %s\n", prog, jname);
                cleanup(1);
            }
        }
        for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
            while (1) {
                for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                    ;
```

```
                if (j < 0 && dx[dmax].offset && fj) {
                        (void) lseek(fd, dx[dmax].offset, 0);
                        (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
                        (void) read(fd, (char *)&dx[dmax].offset,
sizeof(dx[dmax].offset));
                        dx[dmax].ijmp = MAXJMP-1;
                }
                else
                        break;
        }
        if (i >= JMPS) {
                fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                cleanup(1);
        }
        if (j >= 0) {
                siz = dx[dmax].jp.n[j];
                xx = dx[dmax].jp.x[j];
                dmax += siz;
                if (siz < 0) {          /* gap in second seq */
                        pp[1].n[i1] = -siz;
                        xx += siz;

                        /* id = xx - yy + len1 - 1
                         */
                        pp[1].x[i1] = xx - dmax + len1 - 1;
                        gapy++;
                        ngapy -= siz;
/* ignore MAXGAP when doing endgaps */
                        siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
                        i1++;
                }
                else if (siz > 0) {     /* gap in first seq */
                        pp[0].n[i0] = siz;
```

```
                    pp[0].x[i0] = xx;
                    gapx++;
                    ngapx += siz;
/* ignore MAXGAP when doing endgaps */
                    siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                    i0++;
                }
            }
            else
                break;
        }

        /* reverse the order of jmps
         */
        for (j = 0, i0--; j < i0; j++, i0--) {
            i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
            i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
        }
        for (j = 0, i1--; j < i1; j++, i1--) {
            i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
            i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
        }
        if (fd >= 0)
            (void) close(fd);
        if (fj) {
            (void) unlink(jname);
            fj = 0;
            offset = 0;
        }
}
```

```
/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
writejmps(ix)                                                    writejmps
        int     ix;
{
        char    *mktemp();

        if (!fj) {
                if (mktemp(jname) < 0) {
                        fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
                        cleanup(1);
                }
                if ((fj = fopen(jname, "w")) == 0) {
                        fprintf(stderr, "%s: can't write %s\n", prog, jname);
                        exit(1);
                }
        }
        (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}
```

Example calculations for determining % amino acid sequence identity and nucleic acid sequence identity:

1.

PRO	XXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 15 = 33.3%

2.

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 10 = 50%

3.

PRO-DNA	NNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

4.

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

4 divided by 12 = 33.3%

Although the foregoing refers to particular embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments without diverting from the overall concept of the invention. All such modifications are intended to be within the scope of the present invention.

What is claimed is:

CLAIMS

1. A method of detecting of high-grade dysplasia (HGD) in cells of a tissue sample, the method comprising:

(a) obtaining a test tissue sample suspected of comprising cells exhibiting HGD;

(b) establishing the level of expression in the test tissue sample of at least eight genes selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity, wherein the tissue is from esophagus or colon; and

(c) comparing expression of the at least eight genes to a baseline expression of the genes in normal tissue controls of the same tissue type, wherein an increase of at least 1.5-fold in expression of the genes relative to the baseline expression indicates that cells of the test sample exhibit HGD.

2. The method of claim 1, wherein the tissue is human tissue.

3. A method of identifying a esophageal tissue susceptable to esophageal adenocarcoma, comprising detecting esophageal HGD in a test tissue sample according to claim 1.

4. A method according to claim 1, wherein an increase of at least 2-fold in expression of genes relative to the baseline is observed.

5. A method according to claim 1, wherein at least one of the at least eight genes is selected from the group consisting of AGR2 (SEQ ID NO:3), TM7SF1 (SEQ ID NO:13), MAT2B (SEQ ID NO:17), SLNAC1 (SEQ ID NO:23), and TCF4 (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity.

6. A method for determining predisposition of a mammalian tissue to a neo-plastic transformation by detecting HGD in cells of the tissue, the method comprising determining in a cell from the tissue expression of a nucleic acid sequence of at least eight genes selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity, wherein the tissue of from esophagus or colon, and wherein the expression in the test sample is at least 1.5-fold above baseline expression in a normal tissue control of the same tissue type.

7. A method according to claim 6, wherein the tissue is human tissue.

8. A method according to claim 6, wherein at least one of the at least eight genes is selected from the group consisting of AGR2 (SEQ ID NO:3), TM7SF1 (SEQ ID NO:13), MAT2B (SEQ ID NO:17), SLNAC1 (SEQ ID NO:23), and TCF4 (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity.

9. A method of detecting high-grade dysplasia (HGD) in cells of a mammalian tissue sample, the method comprising:

(a) obtaining a test tissue sample suspected of comprising cells exhibiting HGD;

(b) establishing the level of expression in the test tissue sample of at least eight polypeptides encoded by genes selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity, wherein the tissue is from esophagus or colon; and

(c) comparing expression of the at least eight polypeptides in the test tissue sample to expression of the at least eight polypeptides in normal tissue controls of the same tissue type, wherein an increase of at least 1.5-fold in expression of the polypeptides in the test tissue

sample relative to the normal tissue controls indicates that cells of the test sample exhibit HGD.

10. A method as according to claim 9 comprising contacting the test tissue sample with an antibody that specifically binds one of the at least eight polypeptides under conditions that permit the antibody to bind the polypeptide.

11. A method according to claim 9, wherein at least one of the at least eight polypeptides expressed by a gene selected from the group consisting of AGR2 (SEQ ID NO:3), TM7SF1 (SEQ ID NO:13), MAT2B (SEQ ID NO:17), SLNAC1 (SEQ ID NO:23), and TCF4 (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity.

12. The method of claim 1, wherein gene expression is determined by nucleic acid microarray analysis.

13. The method of claim 12, wherein analysis comprises contacting nucleic acid from a test tissue sample with a nucleic acid microarray comprising nucleic acid probe sequences, wherein at least eight of the nucleic acid probe sequences separately comprises at least 50 contiguous nucleotides from a gene selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase

(Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity..

14. The method of claim 13, wherein the at least eight nucleic acid probe sequences comprise at least 60 contiguous nucleotides from a gene selected from the group.

15. The method of claim 14, wherein the at least eight nucleic acid probe sequences comprise at least 80 contiguous nucleotides from a gene selected from the group.

16. The method of claim 15, wherein the at least eight nucleic acid probe sequences comprise at least 100 contiguous nucleotides from a gene selected from the group.

17. The method of claim 16, wherein the at least eight nucleic acid probe sequences comprise at least 150 contiguous nucleotides from a gene selected from the group.

18. The method of claim 17, wherein the at least eight nucleic acid probe sequences comprise at least 200 contiguous nucleotides from a gene selected from the group.

19. The method of claim 13, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least ten genes selected from the group.

20. The method of claim 19, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least twelve genes selected from the group.

21. The method of claim 20, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least fifteen genes selected from the group.

22. The method of claim 21, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least eighteen genes selected from the group.

23. The method of claim 22, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least twenty genes selected from the group.

24. The method of claim 23, wherein the nucleic acid microarray comprises nucleic acid probe sequences from at least twenty two genes selected from the group.

25. The method of claim 1, wherein gene expression is determined by nucleic acid hybridization under high stringency conditions of a detectable probe comprising at least 50 contiguous nucleotides from a gene selected from the group to nucleic acid of cells of the test tissue sample relative to cells of the normal tissue control.

26. The method of claim 25, wherein the hybridization is *in situ* hybridization.

27. The method of claim 26, wherein the hybridization is fluorescent *in situ* hybridization.

28. The method of claim 1, wherein gene expression is determined by polymerase chain reaction (PCR) analysis.

29. The method of claim 1, wherein gene expression is determined by real-time polymerase chain reaction (RT-PCR) analysis.

30. The method of claim 1, wherein gene expression is determined by Taqman® polymerase chain reaction analysis.

31. A kit comprising a microarray, the microarray comprising nucleic acid probe sequences, wherein at least eight of the nucleic acid probe sequences each comprise at least 50 contiguous nucleotides from a gene selected from the group consisting of ET-1 (endothelin-1, NM_001955) (SEQ ID NO:1); AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408) (SEQ ID NO:3); ADAM8 (NM_001109) (SEQ ID NO:5); PRSS8 (Prostasin precursor, serine protease, NM_002773) (SEQ ID NO:7); AXO1 (Axonin-1 precursor, NM_005076) (SEQ ID NO:9); NROB2 (Nuclear hormone receptor, NM_021969) (SEQ ID NO:11); TM7SF1 (NM_003272) (SEQ ID NO:13); DLDH (dihydrolipamide dehydrogenase, NM_000108) (SEQ ID NOS:15); MAT2B (methionine adenosyltransferase II, beta, NM_013283) (SEQ ID NO:17); STC-2 (stanniocalcin-2, NM_003714) (SEQ ID NO:19); PPBI (alkaline phosphatase, intestinal precursor, NM_001631) (SEQ ID NO:21); SLNAC1 (sodium channel receptor SLNAC1, NM_004769) (SEQ ID NO:23); CAH4 (carbonic

anhydrase iv precursor, NM_000717) (SEQ ID NO:25); PA21 (phopholipase a2 precursor, NM_000928) (SEQ ID NO:27); PAR2 (proteinase activated receptor 2 precursor, NM_005242) (SEQ ID NO:29); IDE (insulin-degrading enzyme, NM_004969) (SEQ ID NO:31); MYO1A (myosin-1A, NM_005379) (SEQ ID NO:33); CYP2J2 (cytochrome P450 monooxygenase, NM_000775) (SEQ ID NO:35); PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214) (SEQ ID NO:37); CYB5 (cytochrome b5, 3' end, NM_001914) (SEQ ID NO:39); COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863) (SEQ ID NO:41); and TCF4 (NM_030756) (SEQ ID NO:43), or variants thereof having at least 80% nucleic acid sequence identity, and a package insert indicating that the microarray is for use in detecting HGD in a test tissue sample, wherein the tissue is from esophagus or colon, and wherein an increase in expression in the test tissue sample of at least 1.5-fold of the at least eight genes relative to a normal tissue control of the same tissue type indicates that cells of the test tissue exhibit HGD.

32. The kit of claim 31, wherein the nucleic acid probe sequences each comprise at least 60 contiguous nucleotides from a gene selected from the group.

33. The kit of claim 32, wherein the nucleic acid probe sequences each comprise at least 80 contiguous nucleotides from a gene selected from the group.

34. The kit of claim 33, wherein the nucleic acid probe sequences each comprise at least 100 contiguous nucleotides from a gene selected from the group.

35. The kit of claim 34, wherein the nucleic acid probe sequences each comprise at least 150 contiguous nucleotides from a gene selected from the group.

36. The kit of claim 35, wherein the nucleic acid probe sequences each comprise at least 200 contiguous nucleotides from a gene selected from the group.

37. A method of detecting cancer in a patient, the method comprising:

(a) obtaining a test tissue sample from the patient;

(b) establishing the level of expression of a gene selected from the group consisting of CAD17 (liver-intestine cadherin, NM_004063) (SEQ ID NO:45), CLDN15 (claudin 15, NM_014343) (SEQ ID NO:47), SLNAC1 (sodium channel, NM_004769) (SEQ ID NO:23),

CFTR (chloride channel, NM_000492) (SEQ ID NO:49), H2R (histamine H2 receptor, NM_022304) (SEQ ID NO:51), PRSS8 (serine protease, NM_002773) (SEQ ID NO:7), PA21 (phospholipase A2 group IB, NM_000928) (SEQ ID NO:27), AGR2 (anterior gradient 2 homolog, (NM_006408) (SEQ ID NO:3), EGFR (NM_005228) (SEQ ID NO:53), EPHB2 (NM_004442) (SEQ ID NO:55), CRIPTO CR-1 (NM_003212) (SEQ ID NO:57), Eprin B1 (NM_004429) (SEQ ID NO:59), MMP-17/MT4-MMP (NM_016155) (SEQ ID NO:61), MMP26 (NM_021801) (SEQ ID NO:63), ADAM10 (NM_001110) (SEQ ID NO:65), ADAM8 (NM_001109) (SEQ ID NO:5), ADAM1 (XM_132370) (SEQ ID NO:67), TIM1 (NM_003254) (SEQ ID NO:69), MUC1 (XM_053256) (SEQ ID NO:71), CEA (NM_004363) (SEQ ID NO:73), NCA (NM_002483) (SEQ ID NO:75), Follistatin (NM_006350) (SEQ ID NO:77), Claudin 1 (NM_021101) (SEQ ID NO:79), Claudin 14 (NM_012130) (SEQ ID NO:81), tenascin-R (NM_003285) (SEQ ID NO:83), CAD3 (NM_001793) (SEQ ID NO:85), AXO1 (NM_005076) (SEQ ID NO:9), CONT (NM_001843) (SEQ ID NO:87), Osteopontin (NM_000582) (SEQ ID NO:89), Galectin 8 (NM_006499) (SEQ ID NO:91), PGS1 (bihlycan, NM_001711) (SEQ ID NO:93), Frizzled 2 (NM_001466) (SEQ ID NO.:95), ISLR (NM_005545) (SEQ ID NO:97), FLJ23399 (NM_022763) (SEQ ID NO:99), TEM1 (NM_020404) (SEQ ID NO:101), Tie2 ligand2 (NM_001147) (SEQ ID NO:103), STC-2 (NM_003714) (SEQ ID NO:19), VEGFC (NM_005429) (SEQ ID NO:105), tPA (NM_000930) (SEQ ID NO:107), Endothelin 1 (NM_001955) (SEQ ID NO:1), Thrombomodulin (NM_000361) (SEQ ID NO:109), TF (NM_001993) (SEQ ID NO:111), GPR4 (NM_005282) (SEQ ID NO:113), GPR66 (NM_006056) (SEQ ID NO:115), SLC22A2 (NM_003058) ((SEQ ID NO:117), MLSN1 (NM_002420) (SEQ ID NO:119), and ATN2 (Na/K transport, NM_000702) (SEQ ID NO:121), or variants thereof having at least 80% nucleic acid sequence identity, wherein the test tissue is from esophagus or colon; and wherein the expressing in the test tissue is at a level at least 1.5-fold above expression of the gene in a normal tissue control of the same tissue type.

38. The method of claim 37, wherein inhibition of cell growth is cell death.

39. The method of claim 37, wherein at least two genes selected from the group are expressed at a level at least 1.5-fold above expression of the gene in a normal cell control.

40. The method of claim 39, wherein at least three genes selected from the group are expressed at a level at least 1.5-fold above expression of the gene in a normal cell control.

41. The method of claim 40, wherein at least 5 genes selected from the group are expressed at a level at least 1.5-fold above expression of the gene in a normal cell control.

42. The method of claim 41, wherein at least 8 genes selected from the group are expressed at a level at least 1.5-fold above expression of the gene in a normal cell control.

43. The method of claim 1, wherein the expression p value is less than 0.07.

44. The method of claim 6, wherein the expression p value is less than 0.07.

45. The method of claim 9, wherein the expression p value is less than 0.07.

Figure 1A

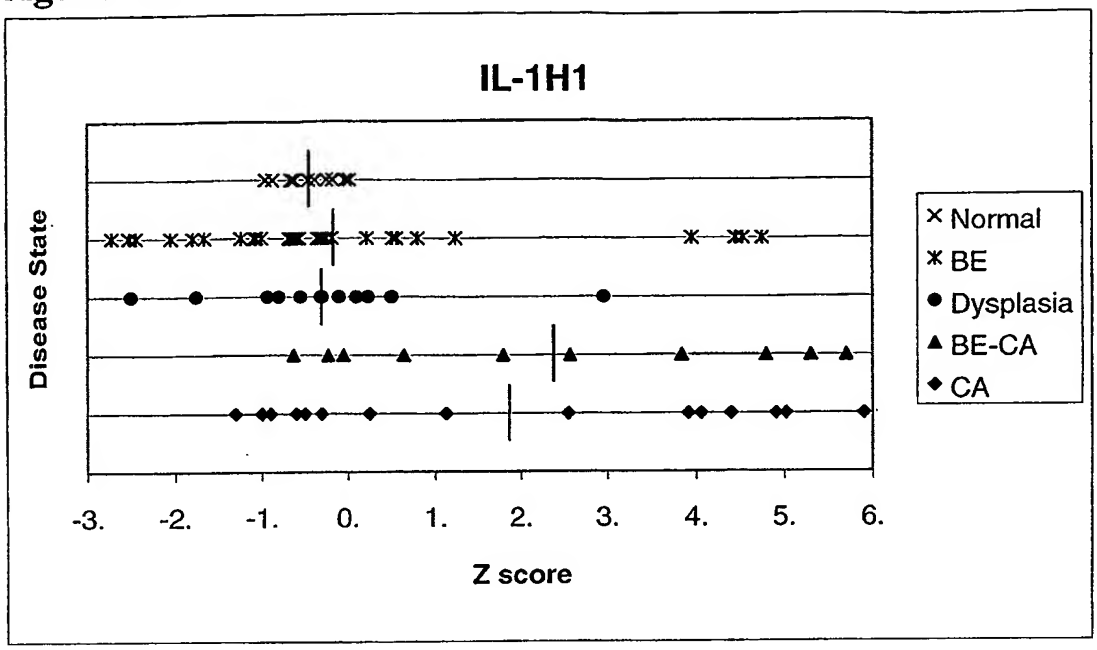


Figure 1B

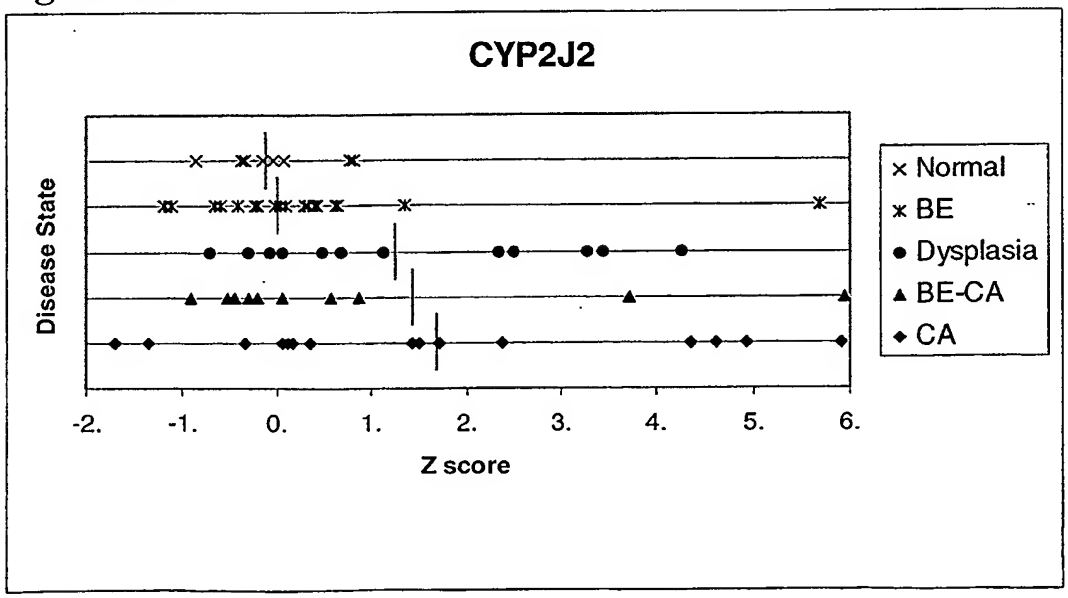


Figure 2A

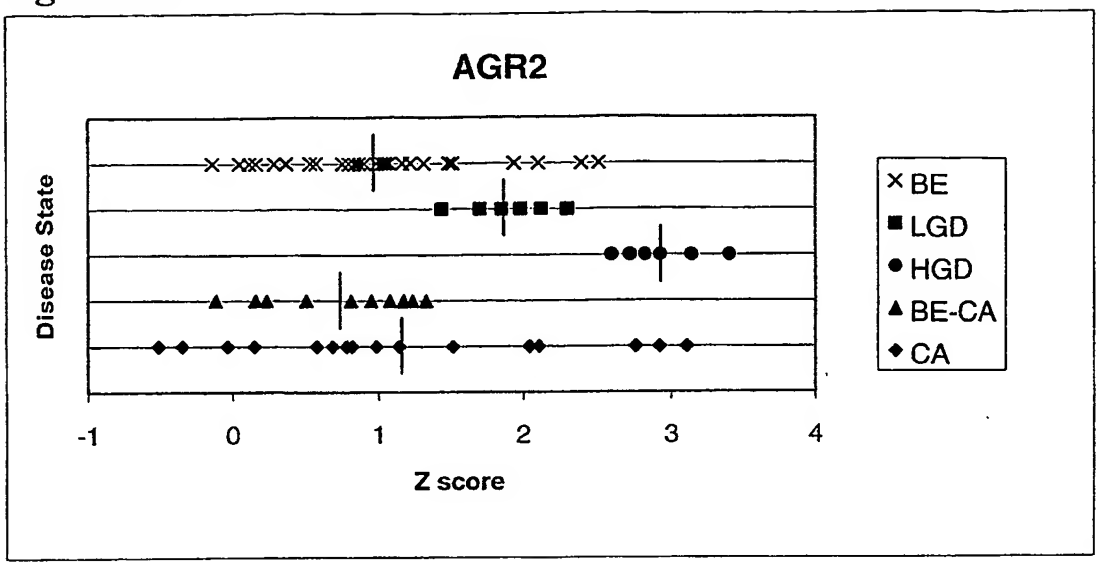


Figure 2B

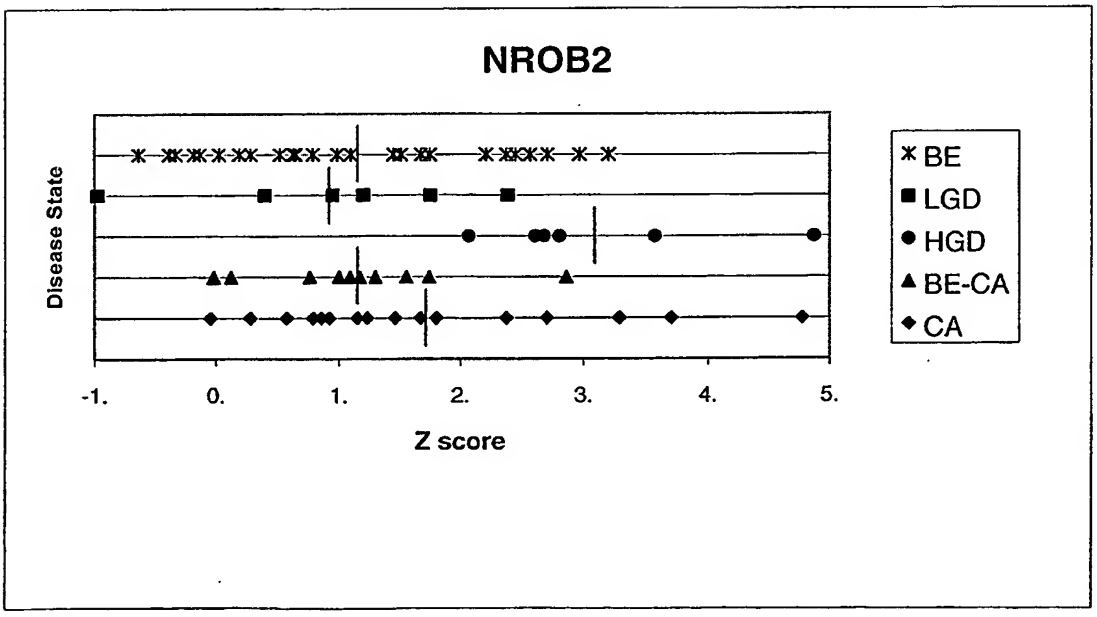


Figure 3A

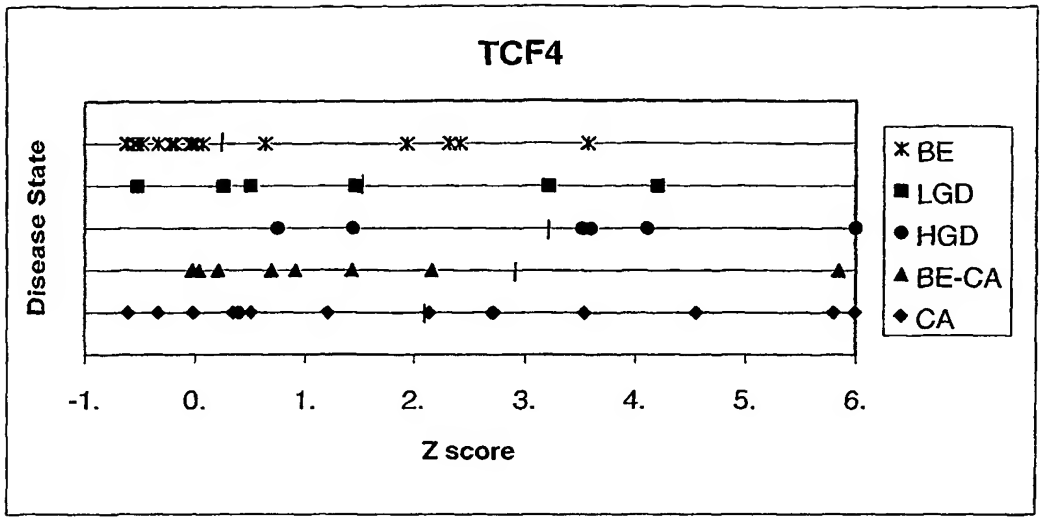
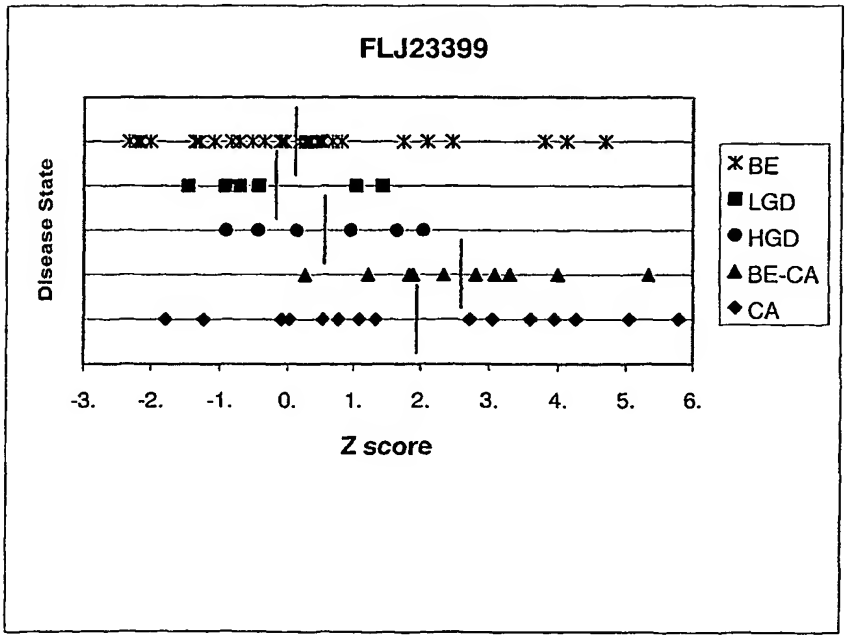


Figure 3B



ET-1 (endothelin-1, NM_001955)

```
   1 cgccgcgtgc gcctgcagac gctccgctcg ctgccttctc tcctggcagg cgctgccttt
  61 tctccccgtt aaagggcact tgggctgaag gatcgctttg agatctgagg aacccgcagc
 121 gctttgaggg acctgaagct gtttttcttc gttttccttt gggttcagtt tgaacgggag
 181 gtttttgatc ccttttttc agaatggatt atttgctcat gattttctct ctgctgtttg
 241 tggcttgcca aggagctcca gaaacagcag tcttaggcgc tgagctcagc gcggtgggtg
 301 agaacggcgg ggagaaaccc actcccagtc caccctggcg gctccgccgg tccaagcgct
 361 gctcctgctc gtccctgatg gataaagagt gtgtctactt ctgccacctg gacatcattt
 421 gggtcaacac tcccgagcac gttgttccgt atggacttgg aagccctagg tccaagagag
 481 ccttggagaa tttacttccc acaaaggcaa cagaccgtga gaatagatgc caatgtgcta
 541 gccaaaaaga caagaagtgc tggaattttt gccaagcagg aaaagaactc agggctgaag
 601 acattatgga gaaagactgg aataatcata agaaaggaaa agactgttcc aagcttggga
 661 aaaagtgtat ttatcagcag ttagtgagag gaagaaaaat cagaagaagt tcagaggaac
 721 acctaagaca aaccaggtcg gagaccatga gaaacagcgt caaatcatct tttcatgatc
 781 ccaagctgaa aggcaatccc tccagagagc gttatgtgac ccacaaccga gcacattggt
 841 gacagacctt cggggcctgt ctgaagccat agcctccacg gagagccctg tggccgactc
 901 tgcactctcc accctggctg ggatcagagc aggagcatcc tctgctggtt cctgactggc
 961 aaaggaccag cgtcctcgtt caaaacattc caagaaaggt taaggagttc ccccaaccat
1021 cttcactggc ttccatcagt ggtaactgct ttggtctctt ctttcatctg gggatgacaa
1081 tggacctctc agcagaaaca cacagtcaca ttcgaattcg ggtggcatcc tccggagaga
1141 gagagaggaa ggagattcca cacaggggtg gagtttctga cgaaggtcct aagggagtgt
1201 ttgtgtctga ctcaggcgcc tggcacattt cagggagaaa ctccaaagtc cacacaaaga
1261 ttttctaagg aatgcacaaa ttgaaaacac actcaaaaga caaacatgca agtaaagaaa
1321 aaaaaaaaaa aaaa (SEQ ID NO:1)
```

FIGURE 4A

ET-1 (endothelin-1, NM_001955)

```
MDYLLMIFSLLFVACQGAPETAVLGAELSAVGENGGEKPTPSPP
RLRRSKRCSCSSLMDKECVYFCHLDIIWVNTPEHVVPYGLGSPRSKRALENLLPTKA
TDRENRCQCASQKDKKCWNFCQAGKELRAEDIMEKDWNNHKKGKDCSKLGKKCIYQQL
VRGRKIRRSSEEHLRQTRSETMRNSVKSSFHDPKLKGNPSRERYVTHNRAHW (SEQ ID NO:2)
```

FIGURE 4B

AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408)

```
   1 ccgcatccta gccgccgact cacacaaggc aggtgggtga ggaaatccag agttgccatg
  61 gagaaaattc cagtgtcagc attcttgctc cttgtggccc tctcctacac tctggccaga
 121 gataccacag tcaaacctgg agccaaaaag gacacaaagg actctcgacc caaactgccc
 181 cagaccctct ccagaggttg gggtgaccaa ctcatctgga ctcagacata tgaagaagct
 241 ctatataaat ccaagacaag caacaaaccc ttgatgatta ttcatcactt ggatgagtgc
 301 ccacacagtc aagctttaaa gaaagtgttt gctgaaaata aagaaatcca gaaattggca
 361 gagcagtttg tcctcctcaa tctggtttat gaaacaactg acaaacacct ttctcctgat
 421 ggccagtatg tccccaggat tatgtttgtt gacccatctc tgacagttag agccgatatc
 481 actggaagat attcaaatcg tctctatgct tacgaacctg cagatacagc tctgttgctt
 541 gacaacatga agaaagctct caagttgctg aagactgaat tgtaaagaaa aaaaatctcc
 601 aagcccttct gtctgtcagg ccttgagact tgaaaccaga agaagtgtga gaagactggc
 661 tagtgtggaa gcatagtgaa cacactgatt aggttatggt ttaatgttac aacaactatt
 721 ttttaagaaa aacaagtttt agaaatttgg tttcaagtgt acatgtgtga aaacaatatt
 781 gtatactacc atagtgagcc atgattttct aaaaaaaaaa ataaatgttt tgggggtgtt
 841 ctgttttctc caacttggtc tttcacagtg gttcgtttac caaataggat taaacacaca
 901 caaaatgctc aaggaaggga caagacaaaa ccaaaactag ttcaaatgat gaagaccaaa
 961 gaccaagtta tcatctcacc acaccacagg ttctcactag atgactgtaa gtagacacga
1021 gcttaatcaa cagaagtatc aagccatgtg ctttagcata aaagaatatt tagaaaaaca
1081 tcccaagaaa atcacatcac tacctagagt caactctggc caggaactct aaggtacaca
1141 ctttcattta gtaattaaat tttagtcaga ttttgcccaa cctaatgctc tcagggaaag
1201 cctctggcaa gtagctttct ccttcagagg tctaatttag tagaaaggtc atccaaagaa
1261 catctgcact cctgaacaca ccctgaagaa atcctgggaa ttgaccttgt aatcgatttg
1321 tctgtcaagg tcctaaagta ctggagtgaa ataaattcag ccaacatgtg actaattgga
1381 agaagagcaa agggtggtga cgtgttgatg aggcagatgg agatcagagg ttactagggt
1441 ttaggaaacg tgaaaggctg tggcatcagg gtaggggagc attctgccta acagaaatta
1501 gaattgtgtg ttaatgtctt cactctatac ttaatctcac attcattaat atatggaatt
1561 cctctactgc ccagcccctc ctgatttctt tggcccctgg actatggtgc tgtatataat
1621 gctttgcagt atctgttgct tgtcttgatt aacttttttg gataaaacct tttttgaaca
1681 gaaaaaaaaa aaaaaaaaaa a (SEQ ID NO:3)
```

FIGURE 5A

AGR2 (anterior gradient 2 (Xenepus laevis) homolog, NM_006408)

```
MEKIPVSAFLLLVALSYTLARDTTVKPGAKKDTKDSRPKLPQTL
SRGWGDQLIWTQTYEEALYKSKTSNKPLMIIHHLDECPHSQALKKVFAENKEIQKLAE
QFVLLNLVYETTDKHLSPDGQYVPRIMFVDPSLTVRADITGRYSNRLYAYEPADTALL
LDNMKKALKLLKTEL (SEQ ID NO:4)
```

FIGURE 5B

ADAM8 (NM_001109)

```
   1 gacccggcca tgcgcggcct cgggctctgg ctgctgggcg cgatgatgct gcctgcgatt
  61 gcccccagcc ggccctgggc cctcatggag cagtatgagg tcgtgttgcc gcggcgtctg
 121 ccaggccccc gagtccgccg agctctgccc tcccacttgg gcctgcaccc agagagggtg
 181 agctacgtcc ttggggccac agggcacaac ttcaccctcc acctgcggaa gaacagggac
 241 ctgctgggtt ccggctacac agagacctat acggctgcca atggctccga ggtgacggag
 301 cagcctcgcg ggcaggacca ctgcttatac cagggccacg tagaggggta cccggactca
 361 gccgccagcc tcagcacctg tgccggcctc aggggtttct tccaggtggg gtcagacctg
 421 cacctgatcg agcccctgga tgaaggtggc gagggcggac ggcacgccgt gtaccaggct
 481 gagcacctgc tgcagacggc cgggacctgc ggggtcagcg acgacagcct gggcagcctc
 541 ctgggacccc ggacggcagc cgtcttcagg cctcggcccg gggactctct gccatcccga
 601 gagacccgct acgtggagct gtatgtggtc gtggacaatg cagagttcca gatgctgggg
 661 agcgaagcag ccgtgcgtca tcgggtgctg gaggtggtga atcacgtgga caagctatat
 721 cagaaactca acttccgtgt ggtcctggtg ggcctggaga tttggaatag tcaggacagg
 781 ttccacgtca gccccgaccc cagtgtcaca ctggagaacc tcctgacctg gcaggcacgg
 841 caacggacac ggcggcacct gcatgacaac gtacagctca tcacgggtgt cgacttcacc
 901 gggactactg tggggtttgc cagggtgtcc gccatgtgct cccacagctc aggggctgtg
 961 aaccaggacc acagcaagaa ccccgtgggc gtggcctgca ccatggccca tgagatgggc
1021 cacaacctgg gcatggacca tgatgagaac gtccagggct gccgctgcca ggaacgcttc
1081 gaggccggcc gctgcatcat ggcaggcagc attggctcca gtttccccag gatgttcagt
1141 gactgcagcc aggcctacct ggagagcttt ttggagcggc cgcagtcggt gtgcctcgcc
1201 aacgcccctg acctcagcca cctggtgggc ggccccgtgt gtgggaacct gtttgtggag
1261 cgtggggagc agtgcgactg cggccccccc gaggactgcc ggaaccgctg ctgcaactct
1321 accacctgcc agctggctga gggggcccag tgtgcgcacg gtacctgctg ccaggagtgc
1381 aaggtgaagc cggctggtga gctgtgccgt cccaagaagg acatgtgtga cctcgaggag
1441 ttctgtgacg gccggcaccc tgagtgcccg gaagacgcct tccaggagaa cggcacgccc
1501 tgctccgggg gctactgcta caacggggcc tgtcccacac tggcccagca gtgccaggcc
1561 ttctgggggc caggtgggca ggctgccgag gagtcctgct tctcctatga catcctacca
1621 ggctgcaagg ccagccggta cagggctgac atgtgtggcg ttctgcagtg caagggtggg
1681 cagcagcccc tggggcgtgc catctgcatc gtggatgtgt gccacgcgct caccacagag
1741 gatggcactg cgtatgaacc agtgcccgag ggcacccggt gtggaccaga gaaggtttgc
1801 tggaaaggac gttgccagga cttacacgtt tacagatcca gcaactgctc tgcccagtgc
1861 cacaaccatg gggtgtgcaa ccacaagcag gagtgccact gccacgcggg ctgggccccg
1921 ccccactgcg cgaagctgct gactgaggtg cacgcagcgt ccgggagcct ccccgtcctc
1981 gtggtggtgg ttctggtgct cctggcagtt gtgctggtca ccctggcagg catcatcgtc
2041 taccgcaaag cccggagccg catcctgagc aggaacgtgg ctcccaagac cacaatgggg
2101 cgctccaacc ccctgttcca ccaggctgcc agccgcgtgc cggccaaggg cggggctcca
2161 gccccatcca ggggccccca agagctggtc cccaccaccc acccgggcca gcccgcccga
2221 cacccggcct cctcggtggc tctgaagagg ccgcccctg ctcctccggt cactgtgtcc
2281 agcccaccct tcccagttcc tgtctacacc cggcaggcac caaagcaggt catcaagcca
2341 acgttcgcac ccccagtgcc cccagtcaaa cccggggctg gtgcggccaa ccctggtcca
2401 gctgagggtg ctgttggccc aaaggttgcc ctgaagcccc ccatccagag gaagcaagga
2461 gccggagctc ccacagcacc ctaggggggc acctgcgcct gtgtggaaat ttggagaagt
2521 tgcggcagag aagccatgcg ttccagcctt ccacggtcca gctagtgccg ctcagcccta
2581 gaccctgact ttgcaggctc agctgctgtt ctaacctcag taatgcatct acctgagagg
2641 ctcctgctgt ccacgccctc agccaattcc ttctccccgc cttggccacg tgtagcccca
2701 gctgtctgca ggcaccaggc tgggatgagc tgtgtgcttg cgggtgcgtg tgtgtgtacg
2761 tgtctccagg tggccgctgg tctcccgctg tgttcaggag gccacatata cagcccctcc
2821 cagccacacc tgcccctgct ctggggcctg ctgagccggc tgccctgggc acccggttcc
2881 aggcagcaca gacgtggggc atccccagaa agactccatc ccaggaccag gttccctcc
2941 gtgctcttcg agagggtgtc agtgagcaga ctgcacccca agctcccgac tccaggtccc
3001 ctgatcttgg gcctgtttcc catgggattc aagagggaca gccccagctt tgtgtgtgtt
3061 taagcttagg aatgcccttt atggaaaggg ctatgtggga gagtcagcta tcttgtctgg
3121 ttttcttgag acctcagatg tgtgttcagc agggctgaaa gcttttattc tttaataatg
3181 agaaatgtat attttactaa taaattattg accgagttct gtagattctt gttaga (SEQ
ID NO:5)
```

FIGURE 6A

ADAM8 (NM_001109)

MRGLGLWLLGAMMLPAIAPSRPWALMEQYEVVLPRRLPGPRVRR
ALPSHLGLHPERVSYVLGATGHNFTLHLRKNRDLLGSGYTETYTAANGSEVTEQPRGQ
DHCLYQGHVEGYPDSAASLSTCAGLRGFFQVGSDLHLIEPLDEGGEGGRHAVYQAEHL
LQTAGTCGVSDDSLGSLLGPRTAAVFRPRPGDSLPSRETRYVELYVVVDNAEFQMLGS
EAAVRHRVLEVVNHVDKLYQKLNFRVVLVGLEIWNSQDRFHVSPDPSVTLENLLTWQA
RQRTRRHLHDNVQLITGVDFTGTTVGFARVSAMCSHSSGAVNQDHSKNPVGVACTMAH
EMGHNLGMDHDENVQGCRCQERFEAGRCIMAGSIGSSFPRMFSDCSQAYLESFLERPQ
SVCLANAPDLSHLVGGPVCGNLFVERGEQCDCGPPEDCRNRCCNSTTCQLAEGAQCAH
GTCCQECKVKPAGELCRPKKDMCDLEEFCDGRHPECPEDAFQENGTPCSGGYCYNGAC
PTLAQQCQAFWGPGGQAAEESCFSYDILPGCKASRYRADMCGVLQCKGGQQPLGRAIC
IVDVCHALTTEDGTAYEPVPEGTRCGPEKVCWKGRCQDLHVYRSSNCSAQCHNHGVCN
HKQECHCHAGWAPPHCAKLLTEVHAASGSLPVLVVVVLVLLAVVLVTLAGIIVYRKAR
SRILSRNVAPKTTMGRSNPLFHQAASRVPAKGGAPAPSRGPQELVPTTHPGQPARHPA
SSVALKRPPPAPPVTVSSPPFPVPVYTRQAPKQVIKPTFAPPVPPVKPGAGAANPGPA
EGAVGPKVALKPPIQRKQGAGAPTAP (SEQ ID NO:6)

FIGURE 6B

PRSS8 (Prostasin precursor, serine protease, NM_002773)

```
   1 gactttggtg gcaagaggag ctggcggagc ccagccagtg ggcggggcca ggggaggggc
  61 gggcaggtag gtgcagccac tcctgggagg accctgcgtg gccagacggt gctggtgact
 121 cgtccacact gctcgcttcg gatactccag gcgtctcccg ttgcggccgc tccctgcctt
 181 agaggccagc cttggacact tgctgccctt ttccagcccg gattctggga tccttccctc
 241 tgagccaaca tctgggtcct gccttcgaca ccaccccaag gcttcctacc ttgcgtgcct
 301 ggagtctgcc ccaggggccc ttgtcctggg ccatggccca gaagggggtc ctggggcctg
 361 ggcagctggg ggctgtggcc attctgctct atcttggatt actccggtcg gggacaggag
 421 cggaaggggc agaagctccc tgcggtgtgg ccccccaagc acgcatcaca ggtggcagca
 481 gtgcagtcgc cggtcagtgg ccctggcagg tcagcatcac ctatgaaggc gtccatgtgt
 541 gtggtggctc tctcgtgtct gagcagtggg tgctgtcagc tgctcactgc ttccccagcg
 601 agcaccacaa ggaagcctat gaggtcaagc tgggggccca ccagctagac tcctactccg
 661 aggacgccaa ggtcagcacc ctgaaggaca tcatccccca ccccagctac ctccaggagg
 721 gctcccaggg cgacattgca ctcctccaac tcagcagacc catcaccttc tcccgctaca
 781 tccggcccat ctgcctccct gcagccaacg cctccttccc caacggcctc cactgcactg
 841 tcactggctg gggtcatgtg gccccctcag tgagcctcct gacgcccaag ccactgcagc
 901 aactcgaggt gcctctgatc agtcgtgaga cgtgtaactg cctgtacaac atcgacgcca
 961 agcctgagga gccgcacttt gtccaagagg acatggtgtg tgctggctat gtggaggggg
1021 gcaaggacgc ctgccagggt gactctgggg gcccactctc ctgccctgtg gagggtctct
1081 ggtacctgac gggcattgtg agctggggag atgcctgtgg ggcccgcaac aggcctggtg
1141 tgtacactct ggcctccagc tatgcctcct ggatccaaag caaggtgaca gaactccagc
1201 ctcgtgtggt gccccaaacc caggagtccc agcccgacag caacctctgt ggcagccacc
1261 tggccttcag ctctgcccca gcccagggct tgctgaggcc catccttttc ctgcctctgg
1321 gcctggctct gggcctcctc tccccatggc tcagcgagca ctgagctggc cctacttcca
1381 ggatggatgc atcacactca aggacaggag cctggtcctt ccctgatggc ctttggaccc
1441 agggcctgac ttgagccact ccttccttca ggactctgcg ggaggctggg gccccatctt
1501 gatctttgag cccattcttc tgggtgtgct ttttgggacc atcactgaga gtcaggagtt
1561 ttactgcctg tagcaatggc cagagcctct ggcccctcac ccaccatgga ccagcccatt
1621 ggccgagctc ctggggagct cctgggaccc ttggctatga aaatgagccc tggctcccac
1681 ctgtttctgg aagactgctc ccggcccgcc tgcccagact gatgagcaca tctctctgcc
1741 ctctccctgt gttctgggct ggggccacct ttgtgcagct tcgaggacag gaaaggcccc
1801 aatcttgccc actggccgct gagcgccccc gagccctgac tcctggactc cggaggactg
1861 agcccccacc ggaactgggc tggcgcttgg atctggggtg ggagtaacag ggcagaaatg
1921 attaaaatgt ttgagcac (SEQ ID NO:7)
```

Figure 7A

PRSS8 (Prostasin precursor, serine protease, NM_002773)

MAQKGVLGPGQLGAVAILLYLGLLRSGTGAEGAEAPCGVAPQAR
ITGGSSAVAGQWPWQVSITYEGVHVCGGSLVSEQWVLSAAHCFPSEHHKEAYEVKLGA
QLDSYSEDAKVSTLKDIIPHPSYLQEGSQGDIALLQLSRPITFSRYIRPICLPAANA
SFPNGLHCTVTGWGHVAPSVSLLTPKPLQQLEVPLISRETCNCLYNIDAKPEEPHFVQ
EDMVCAGYVEGGKDACQGDSGGPLSCPVEGLWYLTGIVSWGDACGARNRPGVYTLASS
YASWIQSKVTELQPRVVPQTQESQPDSNLCGSHLAFSSAPAQGLLRPILFLPLGLALG
LLSPWLSEH (SEQ ID NO:8)

Figure 7B

AXO1 (Axonin-1 precursor, NM_005076)

```
   1 acacacacgc gccctcaccc gccaccgccg ccgcggccgc cgccgcaccc ggacagcgag
  61 cggctgaggc cgccagggcc caaaggacag cggcccagac aggggctggc ggcccggccg
 121 gccccggctc accgactcgg gcagcatcca cctgccccag ccaacaccct tctctcgccc
 181 caggtccttt ctcagcctcc agctgggctg tccccaagct gagctgaggc tcttctcctc
 241 cgatccccac ctctgcccgg acatccacca tggggacagc caccaggagg aagccacacc
 301 tgctgctggt agctgctgtg gcccttgtct cctcttcagc ttggagttca gccctgggat
 361 cccaaaccac cttcgggcct gtctttgaag accagccccc cagtgtgcta ttcccagagg
 421 agtccacgga ggagcaggtg ttgctggcat gccgcgcccg ggccagccct ccagccacct
 481 atcggtggaa gatgaatggt accgagatga agctggagcc aggttcccgt caccagctgg
 541 tgggggggcaa cctggtcatc atgaacccca ccaaggcaca ggatgccggg gtctaccagt
 601 gcctggcctc caacccagtg ggcaccgttg tcagcaggga ggccatcctc cgcttcggct
 661 ttctgcagga attctccaag gaggagcgag acccagtgaa agctcatgaa ggctgggggg
 721 tgatgttgcc ctgtaaccca cctgcccact acccaggctt gtcctaccgc tggctcctca
 781 acgagttccc caacttcatc ccgacggacg ggcgtcactt cgtgtcccag accacaggga
 841 acctgtacat tgcccgaacc aatgcctcag acctgggcaa ctactcctgt ttggccacca
 901 gccacatgga cttctccacc aagagcgtct tcagcaagtt tgctcagctc aacctggctg
 961 ctgaagatac ccggctcttt gcacccagca tcaaggcccg gttcccagca gagacctatg
1021 cactggtggg gcagcaggtc accctggagt gcttcgcctt tgggaaccct gtcccccgga
1081 tcaagtggcg caaagtggac ggctccctgt ccccgcagtg gaccacagct gagcccaccc
1141 tgcagatccc cagcgtcagc tttgaggatg agggcaccta cgagtgtgag gcggagaact
1201 ccaagggccg agacaccgtg cagggccgca tcatcgtgca ggctcagcct gagtggctaa
1261 aagtgatctc ggacacagag gctgacattg gctccaacct gcgttggggc tgtgcagccg
1321 ccggcaagcc ccggcctaca gtgcgctggc tgcggaacgg ggagcctctg gcctcccaga
1381 accgggtgga ggtgttggct ggggacctgc ggttctccaa gctgagcctg gaagactcgg
1441 gcatgtacca gtgtgtggca gagaataagc acggtaccat ctacgccagc gccgagctag
1501 ccgtgcaagc actcgccccc gacttcaggc tgaatcccgt gaggcgtctg atccccgcgg
1561 cccgcggggg agagatcctt atcccctgcc agccccgggc agctccaaag gccgtggtgc
1621 tctggagcaa aggcacggag attttggtca acagcagcag agtgactgta actccagatg
1681 gcaccttgat cataagaaac atcagccggt cagatgaagg caaatacacc tgctttgctg
1741 agaacttcat gggcaaagcc aacagcactg gaatcctatc tgtgcgagat gcaaccaaaa
1801 tcactctagc cccctcaagt gccgacatca acttgggtga caacctgacc ctacagtgcc
1861 atgcctccca cgaccccacc atggacctca ccttcacctg gaccctggac gacttcccca
1921 tcgactttga taagcctgga gggcactacc ggagaactaa tgtgaaggag accattgggg
1981 atctgaccat cctgaacgcc cagctgcgcc atgggggaa gtacacgtgc atggcccaga
2041 cggtggtgga cagcgcgtcc aaggaggcca cagtcctggt ccgaggtccg ccaggtcccc
2101 caggaggtgt ggtggtgagg gacattggcg acaccaccat ccagctcagc tggagccgtg
2161 gcttcgacaa ccacagcccc atcgctaagt acaccctgca agctcgcact ccacctgcag
2221 ggaagtggaa gcaggttcgg accaatcctg caaacatcga gggcaatgcc gagactgcac
2281 aggtgctggg cctcaccccc tggatggact atgagttccg ggtcatagcc agcaacattc
2341 tgggcactgg ggagcctagt gggccctcca gcaaaatccg gaccagggaa gcagcccccc
2401 cggtggcacc ctcaggactc agcggaggag gtggagcccc cggagagctc atcgtcaact
2461 ggacgcccat gtcacgggag taccagaacg gagacggctt cggctacctg ctgtccttcc
2521 gcaggcaggg cagcactcac tggcagaccg cccgggtgcc tggcgccgat gcccagtact
2581 ttgtctacag caacgagagc gtccggccct acacgccctt tgaggtcaag atccgcagct
2641 acaaccgccg cggggatggg cccgagagcc tcactgcact cgtgtactca gctgaggaag
2701 agcccagggt ggcccctacc aaggtgtggg ccaaaggggt ctcatcctca gagatgaacg
2761 tgacctggga acccgtgcag caggacatga atggtatcct cctggggtat gagatccgct
2821 actggaaagc tggggacaaa gaagcagctg cggaccgagt gaggacagca gggctggaca
2881 ccagtgcccg agtcagcggc ctgcatccca acaccaagta ccatgtgacc gtgagggcct
2941 acaaccgggc tggcactggg cctgccagcc cttctgccaa cgccacgacc atgaagcccc
3001 ctccgcggcg acctcctggc aacatctcct ggactttctc aagctctagt cttagcatta
3061 agtgggaccc tgtggtccct ttccgaaatg agtctgcagt caccggctat aagatgctgt
```

FIGURE 8A

3121 accagaatga cttacacctg actcccacgc tccacctcac cggcaagaac tggatagaaa
3181 tcccagtgcc tgaagacatt ggccatgccc tggtacaaat tcggaccaca gggcccggag
3241 gggatgggat ccctgcagaa gtccacatcg tgaggaatgg aggcacaagc atgatggtgg
3301 agaacatggc agtccgccca gcaccacacc ctggcaccgt catttcccac tccgtggcga
3361 tgctgatcct cataggctcc ctggagctct gatcctggaa ccccteeetc tgcgccgcag
3421 ctggacgcca cctccgacgg acacagccag ccccttcctg ctgccaaggt ggcctgacac
3481 tgtgccagag agtggctggt tttaaatacc tactttaaac agtgcccttt ttgtaggagg
3541 taggatattt tatattctgc cgcaggatag aacccacgca aggattttct ttaaattgag
3601 aggcaccagg cagtaacttc catgatgaca ctgacgccta tacctgagct ctaggctgcc
3661 tggagggaag gaacaggccc atgggaagaa gggggtttta aaaacatgtc ttcaactcag
3721 cagagatggc cctctgggac cctatacgga ctccgccact tgagagcagt cctaggcccg
3781 gcaggaacac cagacatgaa caggttgaag aactggagcg aagtgcacac ctcaccatcc
3841 ttcagtctaa ggaagaaggg caagccctgg gaccaagagc tctcccgcct tctccctcga
3901 gcagcagcaa ggaccctgac gctgtccccg ataactccct aggggctcct gcctgcccaa
3961 gcggctgaga accagcgccc cgatgcctga ggctgggagc ctgagcccct tcagctttga
4021 ggggggtgat actccaggct gtttggggtg ggagccaaaa agagttgaga ggccagggcc
4081 cttggtggaa aggggcacca gccttggtct gagatagtca caacccaggt gacgatgccc
4141 tctcagccaa cactgccaac ctgaccctgt catcccgatt gacagcgcca cttcaggtgg
4201 ctgggtgact aaagggcttg tcttggtggg gtctcccacc cctccaagac ccattctgca
4261 cagtccctcc agggtttggg caggagatgg ccaatcatgc gcccacctct ccagtgctgc
4321 ctgcagtcag ctcggcctcc ccgacctgca gccccagact ctgctctccc agcactgact
4381 cactcctgcc tgggagggga atgcagcatt catgctgtgt gtcctggtat tgggaggttt
4441 ctgggaaggg cagaggataa atgtggccct gcctgctccc aggtatacct aggaccacct
4501 ggccagatcc gctcccagac ggccttggac tgcttgcatt tccccggaga aaaaggggtt
4561 aataaatggg ccatcctttc ctgagctctg ggtatactac cagtcacaga acgtcagagc
4621 tggaagaagc cttagagctc aacttcttca agcccctcac tttacagatg aggaaatgga
4681 ggtggtccag agagggtctg ggattcccaa ggtcacacag cccagaagag atggggctgg
4741 gttaagaact cgagtcttcc acctttctgt tcaaggctgt ttgtctaccc agaggaagga
4801 ggcactgctg aatggctatg gcctggctaa gaaggtgatt agtcagtagg gtgtgaaaat
4861 tctacttcaa ggggttcgga ttggtgatca tggggattgg catggctggg ttcccgtcca
4921 aggtgtgggc agagcttcta ccaaacttca acatggaggg ctgacttgaa gctccctgtc
4981 cccctcactc ttgccccaag aaaagaggcc aaagcaagag cagattccct aggcaagagc
5041 agcagcacaa ctaggaaacc ccaaagccca tgctccgaca ggtggccctt cacaggggc
5101 agcgggacag gcatcttgaa gggcatatgt cctcggaagc tccgagcctg ttttctgtag
5161 tttatagtta gagctctatt ttgttatggt tttttaaact tttaagtcct gctctatttt
5221 cctgggcagg tttatgttga tgtttaccca ctacaatttt ttaaaaatat aagctcacat
5281 gccttttccc tgccacagcc aaacccccac tgcaccctac ccacccaccc ctagcccagg
5341 tcagctttcc tggagctggc taatgaaagc ctcctcacct cttcccaacc cttacaagca
5401 agggtgctag gggctcagct atacgaccat tctccctgac agggagtcca aacttggcct
5461 agcatccctc ctggcccccc tctggccacg acttggcctg tgcctggttc tctatcagaa
5521 aggggatgct gaacaaaacc tccttccaag ttttatccaa ttcgttcctc attgcctcgg
5581 gctgcgtcag gggaagcagg ggacaggtgt ccagttgctg ggccgaggga ggagctggtt
5641 tggcatagga cctaaccagt gaagctagag gctacagcca ctaaacttgc ttcaggccaa
5701 cgatagttac tcacaagtaa gtaccttaat gctaatgagg tccactaaaa aggggaggaa
5761 ggcagacctc ctgggagacc cacgaagggt ttttagccag ggaaaactga gccccaggaa
5821 aacctaacca ctgggcaggc agaatttgtt tgagggatag aacgacaaca aaataaatgt
5881 tcctgcagcc tgagatttca ggtagagtac tgactaaggt ttaataagac aataggtgac
5941 ctgaggacat gcaagcttgt aaaatgcaac agcctcctgc tagagtgact tgtacatgag
6001 cttgcttgca gaagactaga ttagatgttt ctcaggatcc cctcctgcgc aggggttctc
6061 tgattttcgt gttctctgcc cagatgggct gggggagttg agagtgtgct tattttcact
6121 gcgatcatga gaccacagtt ctgggttatc tcctctcata catcaagccc cagaggaggc
6181 ggcaagagga acagccacaa acaagtactt taccccacag cttagtggcc agtaaacacc

FIGURE 8B

6241 ctggggacta ggaaaaggaa ccaactgtag gcacctctcc agggcctagg gagacaagtg
6301 tcctctcttc tgcatacatt tgggctcccc ttacagagcc ctttgccctg gctctctggt
6361 ccttgttgct ctaacagtcc agatgtacac ccagcctcag ggggaaggca gctctctcca
6421 gacagagtct cagggcccag caaggtcagg ttatctgctt tcattcaggg caacaaatga
6481 tacaaatggt gccagggagt ggcaaggcca tgggggtagg tgggggtgtc tttttctttt
6541 cataaagtaa caacagacga gactgaggtt aaacatcaga aaaaaacctc tggaatgacc
6601 ttcctcattc caggaggccc tggaataagg aagaggcttc tttctgaggg agctttgagg
6661 aattttgaca gctgttgaca tgggatttgg gaaaggtgaa gctgtgactg gaggggcagg
6721 agatggtcca agtgtccatc cagagatgag actcttagaa tcaaagtgtt cagcccagga
6781 agtcttggag atcccacctt ctgtggccct gcaccttatg ggaagccatt aaggggctc
6841 atctaggaat tctggttaca gcccagtgct catcccagcg tatgctgcct ctttagggca
6901 gccccaaggg ccagccagcc tgtactctgg gcaagagccc aaaatggcta ggaatgtttg
6961 actcccttaa tctcttcccc agctacagag gaatcttttc tctgcctggt ctcagaatgg
7021 gactgccaac tggctcattg gtgggagaca cagtatcctc aaacctgtgg ccactggcat
7081 gacagtggtg ctctgtctcc ctgggtgaca cccaccctag gcttcctcct ggatgtgatg
7141 gggattgcca gagaggctct tagcataaaa ggcattaggt gggcattttt ctgtgtgccc
7201 ccaaaaagct ccatggaaac aggcacctgg tagctgcgga acacccgtgg acttgtgtat
7261 atggtcatag gctttgggaa gacaggacgt aaaggaaaat gagagaaaca aaatgggtca
7321 gatagctttg gccacagccc caggcagcct ttggggccta tgacacttag tgcccttaga
7381 tgggatacat cttgcctcgg ccccaagact cctccaactt acccgtccca tccagggcct
7441 gcacagctta gagaggctca cagcttggca aatgctaggg cttcatcaga ccactgactt
7501 gactcagtgt ttgttaaaat ggaaccactc ccgttggcct actgtttctc tcctgtactt
7561 cttgtaatga tagttattta ttgactctgg tagcaggcag ttcttaaata aagatggttt
7621 ctcaacctgt tggggaaaaa aaaaaaaaaa (SEQ ID NO:9)

Figure 8C

AXO1 (Axonin-1 precursor, NM_005076)

MGTATRRKPHLLLVAAVALVSSSAWSSALGSQTTFGPVFEDQPL
SVLFPEESTEEQVLLACRARASPPATYRWKMNGTEMKLEPGSRHQLVGGNLVIMNPTK
AQDAGVYQCLASNPVGTVVSREAILRFGFLQEFSKEERDPVKAHEGWGVMLPCNPPAH
YPGLSYRWLLNEFPNFIPTDGRHFVSQTTGNLYIARTNASDLGNYSCLATSHMDFSTK
SVFSKFAQLNLAAEDTRLFAPSIKARFPAETYALVGQQVTLECFAFGNPVPRIKWRKV
DGSLSPQWTTAEPTLQIPSVSFEDEGTYECEAENSKGRDTVQGRIIVQAQPEWLKVIS
DTEADIGSNLRWGCAAAGKPRPTVRWLRNGEPLASQNRVEVLAGDLRFSKLSLEDSGM
YQCVAENKHGTIYASAELAVQALAPDFRLNPVRRLIPAARGGEILIPCQPRAAPKAVV
LWSKGTEILVNSSRVTVTPDGTLIIRNISRSDEGKYTCFAENFMGKANSTGILSVRDA
TKITLAPSSADINLGDNLTLQCHASHDPTMDLTFTWTLDDFPIDFDKPGGHYRRTNVK
ETIGDLTILNAQLRHGGKYTCMAQTVVDSASKEATVLVRGPPGPPGGVVVRDIGDTTI
QLSWSRGFDNHSPIAKYTLQARTPPAGKWKQVRTNPANIEGNAETAQVLGLTPWMDYE
FRVIASNILGTGEPSGPSSKIRTREAAPSVAPSGLSGGGGAPGELIVNWTPMSREYQN
GDGFGYLLSFRRQGSTHWQTARVPGADAQYFVYSNESVRPYTPPEVKIRSYNRRGDGP
ESLTALVYSAEEEPRVAPTKVWAKGVSSSEMNVTWEPVQQDMNGILLGYEIRYWKAGD
KEAAADRVRTAGLDTSARVSGLHPNTKYHVTVRAYNRAGTGPASPSANATTMKPPPRR
PPGNISWTFSSSSLSIKWDPVVPFRNESAVTGYKMLYQNDLHLTPTLHLTGKNWIEIP
VPEDIGHALVQIRTTGPGGDGIPAEVHIVRNGGTSMMVENMAVRPAPHPGTVISHSVA
MLILIGSLEL (SEQ ID NO:10)

Figure 8D

NROB2 (Nuclear hormone receptor, NM_021969)

```
   1 gagctggaag tgagagcaga tccctaacca tgagcaccag ccaaccaggg gcctgcccat
  61 gccagggagc tgcaagccgc cccgccattc tctacgcact tctgagctcc agcctcaagg
 121 ctgtcccccg accccgtagc cgctgcctat gtaggcagca ccggcccgtc cagctatgtg
 181 cacctcatcg cacctgccgg gaggccttgg atgttctggc caagacagtg gccttcctca
 241 ggaacctgcc atccttctgg cagctgcctc cccaggacca gcggcggctg ctgcagggtt
 301 gctggggccc cctcttcctg cttgggttgg cccaagatgc tgtgaccttt gaggtggctg
 361 aggccccggt gcccagcata ctcaagaaga ttctgctgga ggagcccagc agcagtggag
 421 gcagtggcca actgccagac agaccccagc cctccctggc tgcggtgcag tggcttcaat
 481 gctgtctgga gtccttctgg agcctggagc ttagccccaa ggaatatgcc tgcctgaaag
 541 ggaccatcct cttcaacccc gatgtgccag gcctccaagc cgcctcccac attgggcacc
 601 tgcagcagga ggctcactgg gtgctgtgtg aagtcctgga accctggtgc ccagcagccc
 661 aaggccgcct gacccgtgtc ctcctcacgg cctccaccct caagtccatt ccgaccagcc
 721 tgcttgggga cctcttcttt cgccctatca ttggagatgt tgacatcgct ggccttcttg
 781 gggacatgct tttgctcagg tgacctgttc cagcccaggc agagatcagg tgggcagagg
 841 ctggcagtgc tgattcagcc tggccatccc cagaggtgac ccaatgctcc tggaggggca
 901 agcctgtata gacagcactt ggctccttag gaacagctct tcactcagcc acaccccaca
 961 ttggacttcc ttggtttgga cacagtgctc cagctgcctg ggaggctttt ggtggtcccc
1021 acagcctctg ggccaagact cctgtccctt cttgggatga gaatgaaagc ttaggctgct
1081 tattggacca gaagtcctat cgactttata cagaactgaa ttaagttatt gatttttgta
1141 ataaaaggta tgaaacacta aaaaaaaa (SEQ ID NO:11)
```

FIGURE 9A

NROB2 (Nuclear hormone receptor, NM_021969)

```
MSTSQPGACPCQGAASRPAILYALLSSSLKAVPRPRSRCLCRQH
RPVQLCAPHRTCREALDVLAKTVAFLRNLPSFWQLPPQDQRRLLQGCWGPLFLLGLAQ
DAVTFEVAEAPVPSILKKILLEEPSSSGGSGQLPDRPQPSLAAVQWLQCCLESFWSLE
LSPKEYACLKGTILFNPDVPGLQAASHIGHLQQEAHWVLCEVLEPWCPAAQGRLTRVL
LTASTLKSIPTSLLGDLFFRPIIGDVDIAGLLGDMLLLR (SEQ ID NO:12)
```

FIGURE 9B

TM7SF1 (NM_003272)

```
   1 cggcgcgatg cgcggagacc cccgcggggg cggcggcggc cgtgagcccc gatgaggccc
  61 gagcgtcccc ggccgcgcgg cagcgccccc ggcccgatgg agaccccgcc gtgggaccca
 121 gcccgcaacg actcgctgcc gcccacgctg accccggccg tgccccccta cgtgaagctt
 181 ggcctcaccg tcgtctacac cgtgttctac gcgctgctct tcgtgttcat ctacgtgcag
 241 ctctggctgg tgctgcgtta ccgccacaag cggctcagct accagagcgt cttcctcttt
 301 ctctgcctct tctgggcctc cctgcggacc gtcctcttct ccttctactt caaagacttc
 361 gtggcggcca attcgctcag ccccttcgtc ttctggctgc tctactgctt ccctgtgtgc
 421 ctgcagtttt tcaccctcac gctgatgaac ttgtacttca cgcaggtgat tttcaaagcc
 481 aagtcaaaat attctccaga attactcaaa taccggttgc ccctctacct ggcctccctc
 541 ttcatcagcc ttgttttcct gttggtgaat ttaacctgtg ctgtgctggt aaagacggga
 601 aattgggaga ggaaggttat cgtctctgtg cgagtggcca ttaatgacac gctcttcgtg
 661 ctgtgtgccg tctctctctc catctgtctc tacaaaatct ctaagatgtc cttagccaac
 721 atttacttgg agtccaaggg ctcctccgtg tgtcaagtga ctgccatcgg tgtcaccgtg
 781 atactgcttt acacctctcg ggcctgctac aacctgttca tcctgtcatt ttctcagaac
 841 aagagcgtcc attcctttga ttatgactgg tacaatgtat cagaccaggc agatttgaag
 901 aatcagctgg gagatgctgg atacgtatta tttggagtgg tgttatttgt ttgggaactc
 961 ttacctacca ccttagtcgt ttatttcttc cgagttagaa atcctacaaa ggaccttacc
1021 aaccctggaa tggtccccag ccatggattc agtcccagat cttatttctt tgacaaccct
1081 cgaagatatg acagtgatga tgaccttgcc tggaacattg cccctcaggg acttcaggga
1141 ggttttgctc cagattacta tgattgggga caacaaacta acagcttcct ggcacaagca
1201 ggaactttgc aagactcaac tttggatcct gacaaaccaa gccttgggta gcatcagtta
1261 acagttttat ggacgattcc tcagatgaaa agcttcagaa aagcatagtg acagctgaat
1321 ttttagggca cttttcctta agaaatagaa cttgattttt atttgttaca ggtttccaat
1381 ggccccatag gaataagcaa taatgtagac tgataaaccc ttattttagt actaaagagg
1441 gagccttgct atttcagtgg gtataattta aacttttaa agaaaatctg tacttttata
1501 aagatgtatt ttgtataact taaataataa tgctaaagta tactagggtt tttttttctt
1561 gagaatgtta ctgcaatcat gttgtagttt gcacagactt ttatgcataa ttcactttaa
1621 aaatatagaa tatatggtct aatagttttt taaagctttt ggactaaagt attccacaaa
1681 tcttacctct ttaggtcact gatggtcact ccgattctga gtgccacatt ggtagactcc
1741 taaaatacag ttgacaactt agccaattgc aactccagtg ttgataatta aaatgaaatg
1801 gtaaagcagc agactgtaag gtctttagag attttttttt aaggttcagg ccgtaggttc
1861 ctcaaggaat ctcttaagtt ttgcccaaag actggtactt cctttcagta gggcgctaat
1921 gtatacacat taatgataag ttgataacat taaaaatgta gctgacttat cctattaaac
1981 ctcctctgct atgttcac (SEQ ID NO:13)
```

FIGURE 10A

TM7SF1 (NM_003272)

```
MRPERPRPRGSAPGPMETPPWDPARNDSLPPTLTPAVPPYVKLG
LTVVYTVFYALLFVFIYVQLWLVLRYRHKRLSYQSVFLFLCLFWASLRTVLFSFYFKD
FVAANSLSPFVFWLLYCFPVCLQFFTLTLMNLYFTQVIFKAKSKYSPELLKYRLPLYL
ASLFISLVFLLVNLTCAVLVKTGNWERKVIVSVRVAINDTLFVLCAVSLSICLYKISK
MSLANIYLESKGSSVCQVTAIGVTVILLYTSRACYNLFILSFSQNKSVHSFDYDWYNV
SDQADLKNQLGDAGYVLFGVVLFVWELLPTTLVVYFFRVRNPTKDLTNPGMVPSHGFS
PRSYFFDNPRRYDSDDDLAWNIAPQGLQGGFAPDYYDWGQQTNSFLAQAGTLQDSTLD
PDKPSLG (SEQ ID NO:14)
```

FIGURE 10B

DLDH (dihydrolipamide dehydrogenase, NM_000108)

```
   1 gcgcagggag gggagacctt ggcggacggc ggagccccag cggaggtgaa agtattggcg
  61 gaaaggaaaa tacagcggaa aaatgcagag ctggagtcgt gtgtactgct ccttggccaa
 121 gagaggccat ttcaatcgaa tatctcatgg cctacaggga ctttctgcag tgcctctgag
 181 aacttacgca gatcagccga ttgatgctga tgtaacagtt ataggttctg gtcctggagg
 241 atatgttgct gctattaaag ctgcccagtt aggcttcaag acagtctgca ttgagaaaaa
 301 tgaaacactt ggtggaacat gcttgaatgt tggttgtatt ccttctaagg ctttattgaa
 361 caactctcat tattaccata tggcccatgg aacagatttt gcatctagag gaattgaaat
 421 gtccgaagtt cgcttgaatt tagacaagat gatggagcag aagagtactg cagtaaaagc
 481 tttaacaggt ggaattgccc acttattcaa acagaataag gttgttcatg tcaatggata
 541 tggaaagata actggcaaaa atcaagtcac tgctacgaaa gctgatggcg gcactcaggt
 601 tattgataca aagaacattc ttatagccac gggttcagaa gttactcctt ttcctggaat
 661 cacgatagat gaagatacaa tagtgtcatc tacaggtgct ttatctttaa aaaaagttcc
 721 agaaaagatg gttgttattg gtgcaggagt aataggtgta gaattgggtt cagtttggca
 781 aagacttggt gcagatgtga cagcagttga atttttaggt catgtaggtg gagttggaat
 841 tgatatggag atatctaaaa actttcaacg catccttcaa aaacaggggt ttaaatttaa
 901 attgaataca aaggttactg gtgctaccaa gaagtcagat ggaaaaattg atgtttctat
 961 tgaagctgct tctggtggta aagctgaagt tatcacttgt gatgtactct tggtttgcat
1021 tggccgacga ccctttacta agaatttggg actagaagag ctgggaattg aactagatcc
1081 tagaggtaga attccagtca ataccagatt tcaaactaaa attccaaata tctatgccat
1141 tggtgatgta gttgctggtc caatgctggc tcacaaagca gaggatgaag gcattatctg
1201 tgttgaagga atggctggtg gtgctgtgca cattgactac aattgtgtgc catcagtgat
1261 ttacacacac cctgaagttg cttgggttgg caaatcagaa gagcagttga aagaagaggg
1321 tattgagtac aaagttggga aattcccatt tgctgctaac agcagagcta agacaaatgc
1381 tgacacagat ggcatggtga agatccttgg gcagaaatcg acagacagag tactgggagc
1441 acatattctt ggaccaggtg ctggagaaat ggtaaatgaa gctgctcttg ctttggaata
1501 tggagcatcc tgtgaagata tagctagagt ctgtcatgca catccgacct tatcagaagc
1561 ttttagagaa gcaaatcttg ctgcgtcatt tggcaaatca atcaactttt gaattagaag
1621 attatatatt ttttttctg aaatttcctg ggagcttttg tagaagtcac attcctgaac
1681 aggatattct cacagctcca agaatttcta ggactgaatt atgaaacttt tggaaggtat
1741 ttaataggtt tggacaaaat ggaatactct tatatctata ttttacataa atttagtatt
1801 ttgtttcagt gcactaatat gtaagacaaa aaggactact tattgtagtc atcctggaat
1861 atctccgtca actcatattt tcatgctgtt catgaaagat tcaatgcccc tgaatttaaa
1921 tagctctttt ctctgataca gaaaagttga attttacatg gctggagcta gaatttgata
1981 tgtgaacagt tgtgtttgaa gcacagtgat caagttattt ttaatttggt tttcacattg
2041 gaaacaagtc agtcattcag atatgattca aatgtctata aaccaaactg atgtaagtaa
2101 atggtctctc acttgtttta tttaacctct aaattctttc attttagggg tagcatttgt
2161 gttgaagagg ttttaaagct tccattgttg tctgcaactc tgaagggtaa ttatatagtt
2221 acccaaatta agagagtcta tttacggaac tcaaatacgt gggcattcaa atgtattaca
2281 gtggggaatg aagatactga aataaacgtc ttaaatattc (SEQ ID NO:15)
```

FIGURE 11A

DLDH (dihydrolipamide dehydrogenase, NM_000108)

```
MQSWSRVYCSLAKRGHFNRISHGLQGLSAVPLRTYADQPIDADV
TVIGSGPGGYVAAIKAAQLGFKTVCIEKNETLGGTCLNVGCIPSKALLNNSHYYHMAH
GTDFASRGIEMSEVRLNLDKMMEQKSTAVKALTGGIAHLFKQNKVVHVNGYGKITGKN
QVTATKADGGTQVIDTKNILIATGSEVTPFPGITIDEDTIVSSTGALSLKKVPEKMVV
IGAGVIGVELGSVWQRLGADVTAVEFLGHVGGVGIDMEISKNFQRILQKQGFKFKLNT
KVTGATKKSDGKIDVSIEAASGGKAEVITCDVLLVCIGRRPFTKNLGLEELGIELDPR
GRIPVNTRFQTKIPNIYAIGDVVAGPMLAHKAEDEGIICVEGMAGGAVHIDYNCVPSV
IYTHPEVAWVGKSEEQLKEEGIEYKVGKFPFAANSRAKTNADTDGMVKILGQKSTDRV
LGAHILGPGAGEMVNEAALALEYGASCEDIARVCHAHPTLSEAFREANLAASFGKSIN
F (SEQ ID NO:16)
```

FIGURE 11B

MAT2B (methionine adenosyltransferase II, beta, NM_013283)

```
   1 gttctgggcc taggggaggc gggccgaggg cgtctgagct gaggcccgcg tcgatcctgg
  61 gttggaggag gtggcggccg ctgaggctgc ggcgtgaaga cggcgggcat ggtggggcgg
 121 gagaaagagc tctctataca ctttgttccc gggagctgtc ggctggtgga ggaggaagtt
 181 aacatcccta ataggagggt tctggttact ggtgccactg ggcttcttgg cagagctgta
 241 cacaaagaat ttcagcagaa taattggcat gcagttggct gtggtttcag aagagcaaga
 301 ccaaaatttg aacaggttaa tctgttggat tctaatgcag ttcatcacat cattcatgat
 361 tttcagcccc atgttatagt acattgtgca gcagagagaa gaccagatgt tgtagaaaat
 421 cagccagatg ctgcctctca acttaatgtg gatgcttctg ggaatttagc aaaggaagca
 481 gctgctgttg gagcatttct catctacatt agctcagatt atgtatttga tggaacaaat
 541 ccaccttaca gagaggaaga cataccagct cccctaaatt tgtatggcaa aacaaaatta
 601 gatggagaaa aggctgtcct ggagaacaat ctaggagctg ctgttttgag gattcctatt
 661 ctgtatgggg aagttgaaaa gctcgaagaa agtgctgtga ctgttatgtt tgataaagtg
 721 cagttcagca acaagtcagc aaacatggat cactggcagc agaggttccc cacacatgtc
 781 aaagatgtgg ccactgtgtg ccggcagcta gcagagaaga gaatgctgga tccatcaatt
 841 aagggaacct ttcactggtc tggcaatgaa cagatgacta agtatgaaat ggcatgtgca
 901 attgcagatg ccttcaacct ccccagcagt cacttaagac ctattactga cagccctgtc
 961 ctaggagcac aacgtccgag aaatgctcag cttgactgct ccaaattgga gaccttgggc
1021 attggccaac gaacaccatt tcgaattgga atcaaagaat cactttggcc tttcctcatt
1081 gacaagagat ggagacaaac ggtctttcat tagtttattt gtgttgggtt ctttttttt
1141 tttaaatgaa aagtatagta tgtggcactt tttaaagaac aaaggaaata gttttgtatg
1201 agtactttaa ttgtgactct taggatcttt caggtaaatg atgctcttgc actagtgaaa
1261 ttgtctaaag aaactaaagg gcagtcatgc cctgtttgca gtaatttttc tttttatcat
1321 tttgtttgtc ctggctaaac ttggagtttg agtatagtaa attatgatcc ttaaatattt
1381 gagagtcagg atgaagcaga tctgctgtag acttttcaga tgaaattgtt cattctcgta
1441 acctccatat tttcaggatt tttgaagctg ttgacctttt catgttgatt attttaaatt
1501 gtgtgaaata gtataaaaat cattggtgtt cattatttgc tttgcctgag ctcagatcaa
1561 aatgtttgaa gaaaggaact ttatttttgc aagttacgta cagtttttat gcttgagata
1621 tttcaacatg ttatgtatat tggaacttct acagcttgat gcctcctgct tttatagcag
1681 tttatgggga gcacttgaaa gagcgtgtgt acatgtattt tttttctagg caaacattga
1741 atgcaaacgt gtatttttt aatataaata tataactgtc cttttcatcc catgttgccg
1801 ctaagtgata tttcatatgt gtggttatac tcataataat gggccttgta agtcttttca
1861 ccattcatga ataataataa atatgtactg ctggcatgta atgcttagtt ttcttgtatt
1921 tacttctttt tttaaatgta aggaccaaac ttctaaacta attgttcttt tgttgcttta
1981 atttttaaaa attacattct tctgatgtaa catgtgatac atacaaaaga atatagttta
2041 atatgtattg aaataaaaca caataaaatt aaaaaaaaaa aaaaaaaaaa (SEQ ID
NO:17)
```

FIGURE 12A

MAT2B (methionine adenosyltransferase II, beta, NM_013283)

```
MVGREKELSIHFVPGSCRLVEEEVNIPNRRVLVTGATGLLGRAV
HKEFQQNNWHAVGCGFRRARPKFEQVNLLDSNAVHHIIHDFQPHVIVHCAAERRPDVV
ENQPDAASQLNVDASGNLAKEAAAVGAFLIYISSDYVFDGTNPPYREEDIPAPLNLYG
KTKLDGEKAVLENNLGAAVLRIPILYGEVEKLEESAVTVMFDKVQFSNKSANMDHWQQ
RFPTHVKDVATVCRQLAEKRMLDPSIKGTFHWSGNEQMTKYEMACAIADAFNLPSSHL
RPITDSPVLGAQRPRNAQLDCSKLETLGIGQRTPFRIGIKESLWPFLIDKRWRQTVFH (SEQ ID
NO:18)
```

FIGURE 12B

STC-2 (stanniocalcin-2, NM_003714)

```
   1 gaggaggagg gaaaaggcga gcaaaaagga agagtgggag gaggagggga agcggcgaag
  61 gaggaagagg aggaggagga agaggggagc acaaaggatc caggtctccc gacgggaggt
 121 taataccaag aaccatgtgt gccgagcggc tgggccagtt catgaccctg gctttggtgt
 181 tggccacctt tgacccggcg cgggggaccg acgccaccaa cccacccgag ggtccccaag
 241 acaggagctc ccagcagaaa ggccgcctgt ccctgcagaa tacagcggag atccagcact
 301 gtttggtcaa cgctggcgat gtggggtgtg gcgtgtttga atgtttcgag aacaactctt
 361 gtgagattcg gggcttacat gggatttgca tgacttttct gcacaacgct ggaaaatttg
 421 atgcccaggg caagtcattc atcaaagacg ccttgaaatg taaggcccac gctctgcggc
 481 acaggttcgg ctgcataagc cggaagtgcc cggccatcag ggaaatggtg tcccagttgc
 541 agcgggaatg ctacctcaag cacgacctgt gcgcggctgc ccaggagaac acccgggtga
 601 tagtggagat gatccatttc aaggacttgc tgctgcacga accctacgtg gacctcgtga
 661 acttgctgct gacctgtggg gaggaggtga aggaggccat cacccacagc gtgcaggttc
 721 agtgtgagca gaactgggga agcctgtgct ccatcttgag cttctgcacc tcggccatcc
 781 agaagcctcc cacggcgccc cccgagcgcc agccccaggt ggacagaacc aagctctcca
 841 gggcccacca cggggaagca ggacatcacc tcccagagcc cagcagtagg gagactggcc
 901 gaggtgccaa gggtgagcga ggtagcaaga gccacccaaa cgcccatgcc cgaggcagag
 961 tcgggggcct tggggctcag ggaccttccg gaagcagcga gtgggaagac gaacagtctg
1021 agtattctga tatccggagg tgaaatgaaa ggcctggcca cgaaatcttt cctccacgcc
1081 gtccattttc ttatctatgg acattccaaa acatttacca ttagagaggg gggatgtcac
1141 acgcaggatt ctgtggggac tgtggacttc atcgaggtgt gtgttcgcgg aacggacagg
1201 tgagatggag acccctgggg ccgtggggtc tcaggggtgc ctggtgaatt ctgcacttac
1261 acgtactcaa gggagcgcgc ccgcgttatc ctcgtacctt tgtcttcttt ccatctgtgg
1321 agtcagtggg tgtcggccgc tctgttgtgg gggaggtgaa ccagggaggg gcagggcaag
1381 gcagggcccc cagagctggg ccacacagtg ggtgctgggc ctcgccccga agcttctggt
1441 gcagcagcct ctggtgctgt ctccgcggaa gtcagggcgg ctggattcca ggacaggagt
1501 gaatgtaaaa ataaatatcg cttagaatgc aggagaaggg tggagaggag gcaggggccg
1561 agggggtgct tggtgccaaa ctgaaattca gtttcttgtg tggggccttg cggttcagag
1621 ctcttggcga gggtggaggg aggagtgtca tttctatgtg taatttctga gccattgtac
1681 tgtctgggct gggggggaca ctgtccaagg gagtggcccc tatgagttta tattttaacc
1741 actgcttcaa atctcgattt cacttttttt atttatccag ttatatctac atatctgtca
1801 tctaaataaa tggctttcaa acaaagcaac tgggtcatta aaaccagctc aaaggggggtt
1861 taaaaaaaaa aaaaccagcc catcctttga ggctgatttt tctttttttt aagttctatt
1921 ttaaaagcta tcaaacagcg acatagccat acatctgact gcctgacatg gactcctgcc
1981 cacttggggg aaaccttata cccagaggaa aatacacacc tggggagtac atttgacaaa
2041 tttcccttag gatttcgtta tctcaccttg accctcagcc aagattggta aagctgcgtc
2101 ctggcgattc caggagaccc agctggaaac ctggcttctc catgtgaggg gatgggaaag
2161 gaaagaagag aatgaagact acttagtaat tcccatcagg aaatgctgac cttttacata
2221 aaatcaagga gactgctgaa aatctctaag ggacaggatt ttccagatcc taattggaaa
2281 tttagcaata aggagaggag tccaagggga caaataaagg cagagagaga gagagagaga
2341 gggagaggaa gaaaagagag agagaaaaga gcctcgtgcc (SEQ ID NO:19)
```

FIGURE 13A

STC-2 (stanniocalcin-2, NM_003714)

```
MCAERLGQFMTLALVLATFDPARGTDATNPPEGPQDRSSQQKGR
LSLQNTAEIQHCLVNAGDVGCGVFECFENNSCEIRGLHGICMTFLHNAGKFDAQGKSF
IKDALKCKAHALRHRFGCISRKCPAIREMVSQLQRECYLKHDLCAAAQENTRVIVEMI
HFKDLLLHEPYVDLVNLLLTCGEEVKEAITHSVQVQCEQNWGSLCSILSFCTSAIQKP
PTAPPERQPQVDRTKLSRAHHGEAGHHLPEPSSRETGRGAKGERGSKSHPNAHARGRV
GGLGAQGPSGSSEWEDEQSEYSDIRR (SEQ ID NO:20)
```

FIGURE 13B

PPBI (alkaline phosphatase, intestinal precursor, NM_001631)

```
   1 gttcctggtg tccccacttc gcctccctcc tgctgccccc aagacatgca ggggccctgg
  61 gtgctgctgc tgctgggcct gaggctacag ctctccctgg gcgtcatccc agctgaggag
 121 gagaacccgg ccttctggaa ccgccaggca gctgaggccc tggatgctgc caagaagctg
 181 cagcccatcc agaaggtcgc caagaacctc atcctcttcc tgggcgatgg gttgggggtg
 241 cccacggtga cagccaccag gatcctaaag gggcagaaga atggcaaact ggggcctgag
 301 acgcccctgg ccatggaccg cttcccatac ctggctctgt ccaagacata caatgtggac
 361 agacaggtgc cagacagcgc agccacagcc acggcctacc tgtgcggggt caaggccaac
 421 ttccagacca tcggcttgag tgcagccgcc cgctttaacc agtgcaacac gacacgcggc
 481 aatgaggtca tctccgtgat gaaccgggcc aagcaagcag gaaagtcagt aggagtggtg
 541 accaccacac gggtgcagca cgcctcgcca gccggcacct acgcacacac agtgaaccgc
 601 aactggtact cagatgctga catgcctgcc tcagcccgcc aggaggggtg ccaggacatc
 661 gccactcagc tcatctccaa catggacatt gacgtgatcc ttggcggagg ccgcaagtac
 721 atgtttccca tggggacccc agaccctgag tacccagctg atgccagcca gaatggaatc
 781 aggctggacg ggaagaacct ggtgcaggaa tggctggcaa agcaccaggg tgcctggtat
 841 gtgtggaacc gcactgagct catgcaggcg tccctggacc agtctgtgac ccatctcatg
 901 ggcctctttg agcccggaga cacgaaatat gagatcctcc gagaccccac actggacccc
 961 tccctgatgg agatgacaga ggctgccctg cgcctgctga gcaggaaccc ccgcggcttc
1021 tacctctttg tggagggcgg ccgcatcgac catggtcatc atgagggtgt ggcttaccag
1081 gcagtcactg aggcggtcat gttcgacgac gccattgaga gggcgggcca gctcaccagc
1141 gaggaggaca cgctgaccct cgtcaccgct gaccactccc atgtcttctc ctttggtggc
1201 tacaccttgc gagggagctc catcttcggg ttggccccca gcaaggctca ggacagcaaa
1261 gcctacacgt ccatcctgta cggcaatggc ccgggctacg tgttcaactc aggcgtgcga
1321 ccagacgtga atgagagcga gagcgggagc cccgattacc agcagcaggc ggcggtgccc
1381 ctgtcgtccg agacccacgg aggcgaagac gtggcggtgt ttgcgcgcgg cccgcaggcg
1441 cacctggtgc atggtgtgca ggagcagagc ttcgtagcgc atgtcatggc cttcgctgcc
1501 tgtctggagc cctacacggc ctgcgacctg gcgctccccg cctgcaccac cgacgccgcg
1561 cacccagttg ccgcgtcgct gccactgctg gccgggaccc tgctgctgct gggggcgtcc
1621 gctgctccct gagtgcccca ctccggagtt atcctgctcc ccacctccgg gcgtcctgcc
1681 ctgttccccg tcctgagccg ccacttccag cgaacacaca caggtgtcct gccgttggac
1741 cttcacctcc tagagataaa ccagcctcag ctggcgcagc ggggcccttc ttccctccgc
1801 atccccttca gggagcagga gcccagggcg ccctgggagc tgagcctggg acttccagga
1861 cctcccctca ggttgttctc tgattcttcc tcccaacccc agagactgca gatttgtgcc
1921 atgcggctgc ctgcacccca gacaataaag ggaccaaaac cacccaaccc ccaccctgcc
1981 tctatcctaa ggaagaccaa gcaggcctgg acccagagac gtcccccatc gtgggacacg
2041 acacacccag accgcgtgcc ccaccgtctt agcttcaatc ctggcagcac ctggtagacc
2101 caaggacttg ggtggatcag gacacctgaa gaagagaagc ttccggcaac cctgcaaccc
2161 acccaaggag gctactggat cggggattcc caggggggct ttgacacagt cctctgctgt
2221 ctccccacta ggatcattcc acacccctgc acctgaccaa gggaccaatg aggcagaggc
2281 ttgccccaag tcacagccac tcagatgctt cctgcccccc agtgcccatt ccaggtcacc
2341 agatccaagg agcgcttgag gagctctggg tacagggcag caacccagag cccatgggcc
2401 ctcccgggac atctggatgc tgggcataga tttctcaaca aggaagactc ccctgcctcc
2461 tcaaggtctc cattctccta ggagacaaag caataataaa aggtgttaga caatgt (SEQ
ID NO:21)
```

FIGURE 14A

PPBI (alkaline phosphatase, intestinal precursor, NM_001631)

```
MQGPWVLLLLGLRLQLSLGVIPAEEENPAFWNRQAAEALDAAKK
LQPIQKVAKNLILFLGDGLGVPTVTATRILKGQKNGKLGPETPLAMDRFPYLALSKTY
NVDRQVPDSAATATAYLCGVKANFQTIGLSAAARFNQCNTTRGNEVISVMNRAKQAGK
SVGVVTTTRVQHASPAGTYAHTVNRNWYSDADMPASARQEGCQDIATQLISNMDIDVI
LGGGRKYMFPMGTPDPEYPADASQNGIRLDGKNLVQEWLAKHQGAWYVWNRTELMQAS
LDQSVTHLMGLFEPGDTKYEILRDPTLDPSLMEMTEAALRLLSRNPRGFYLFVEGGRI
DHGHHEGVAYQAVTEAVMFDDAIERAGQLTSEEDTLTLVTADHSHVFSFGGYTLRGSS
IFGLAPSKAQDSKAYTSILYGNGPGYVFNSGVRPDVNESESGSPDYQQQAAVPLSSET
HGGEDVAVFARGPQAHLVHGVQEQSFVAHVMAFAACLEPYTACDLALPACTTDAAHPV
AASLPLLAGTLLLLGASAAP (SEQ ID NO:22)
```

FIGURE 14B

SLNAC1 (sodium channel receptor SLNAC1, NM_004769)

```
   1 agaattcggc acgacggggt tctggccatg aagcccacct caggcccaga ggaggcccgg
  61 cggccagcct cggacatccg cgtgttcgcc agcaactgct cgatgcacgg gctgggccac
 121 gtcttcgggc caggcagcct gagcctgcgc cgggggatgt gggcagcggc cgtggtcctg
 181 tcagtggcca ccttcctcta ccaggtggct gagagggtgc gctactacag ggagttccac
 241 caccagactg ccctggatga gcgagaaagc caccggctca tcttcccggc tgtcaccctg
 301 tgcaacatca acccactgcg ccgctcgcgc ctaacgccca acgacctgca ctgggctggg
 361 tctgcgctgc tgggcctgga tcccgcagag cacgccgcct tcctgcgcgc cctgggccgg
 421 ccccctgcac cgcccggctt catgcccagt cccacctttg acatggcgca actctatgcc
 481 cgtgctgggc actccctgga tgacatgctg ctggactgtc gcttccgtgg ccaaccttgt
 541 gggcctgaga acttcaccac gatcttcacc cggatgggaa agtgctacac atttaactct
 601 ggcgctgatg gggcagagct gctcaccact actaggggtg gcatgggcaa tgggctggac
 661 atcatgctgg acgtgcagca ggaggaatat ctacctgtgt ggagggacaa tgaggagacc
 721 ccgtttgagg tggggatccg agtgcagatc cacagccagg aggagccgcc catcatcgat
 781 cagctgggct tgggggtgtc cccgggctac cagacctttg tttcttgcca gcagcagcag
 841 ctgagcttcc tgccaccgcc ctggggcgat tgcagttcag catctctgaa ccccaactat
 901 gagccagagc cctctgatcc cctaggctcc cccagcccca gccccagccc tccctatacc
 961 cttatggggt gtcgcctggc ctgcgaaacc cgctacgtgg ctcggaagtg cggctgccga
1021 atggtgtaca tgccaggcga cgtgccagtg tgcagccccc agcagtacaa gaactgtgcc
1081 cacccggcca tagatgccat gcttcgcaag gactcgtgcg cctgccccaa cccgtgcgcc
1141 agcacgcgct acgccaagga gctctccatg gtgcggatcc cgagccgcgc cgccgcgcgc
1201 ttcctggccc ggaagctcaa ccgcagcgag gcctacatcg cggagaacgt gctggccctg
1261 gacatcttct ttgaggccct caactatgag accgtggagc agaagaaggc ctatgagatg
1321 tcagagctgc ttggtgacat tgggggccag atggggctgt tcatcggggc cagcctgctc
1381 accatcctcg agatcctaga ctacctctgt gaggtgttcc gagacaaggt cctgggatat
1441 ttctggaacc gacagcactc ccaaaggcac tccagcacca atctgcttca ggaagggctg
1501 ggcagccatc gaacccaagt tccccacctc agcctgggcc ccagacctcc cacccctccc
1561 tgtgccgtca ccaagactct ctccgcctcc caccgcacct gctaccttgt cacacagctc
1621 tagacctgct gtctgtgtcc tcggagcccc gccctgacat cctggacatg cctagcctgc
1681 acgtagcttt tccgtcttca ccccaaataa agtcctaatg catcaaaaaa aaaaaaaaaa
1741 aaaaaa (SEQ ID NO:23)
```

FIGURE 15A

SLNAC1 (sodium channel receptor SLNAC1, NM_004769)

```
MKPTSGPEEARRPASDIRVFASNCSMHGLGHVFGPGSLSLRRGM
WAAAVVLSVATFLYQVAERVRYYREFHHQTALDERESHRLIFPAVTLCNINPLRRSRL
TPNDLHWAGSALLGLDPAEHAAFLRALGRPPAPPGFMPSPTFDMAQLYARAGHSLDDM
LLDCRFRGQPCGPENFTTIFTRMGKCYTFNSGADGAELLTTTRGGMGNGLDIMLDVQQ
EEYLPVWRDNEETPFEVGIRVQIHSQEEPPIIDQLGLGVSPGYQTFVSCQQQQLSFLP
PPWGDCSSASLNPNYEPEPSDPLGSPSPSPSPPYTLMGCRLACETRYVARKCGCRMVY
MPGDVPVCSPQQYKNCAHPAIDAMLRKDSCACPNPCASTRYAKELSMVRIPSRAAARF
LARKLNRSEAYIAENVLALDIFFEALNYETVEQKKAYEMSELLGDIGGQMGLFIGASL
LTILEILDYLCEVFRDKVLGYFWNRQHSQRHSSTNLLQEGLGSHRTQVPHLSLGPRPP
PPCAVTKTLASHRTCYLVTQL (SEQ ID NO:24)
```

FIGURE 15B

CAH4 (carbonic anhydrase iv precursor, NM_000717)

```
   1 ctcggtgcgc gaccccggct cagaggactc tttgctgtcc cgcaagatgc ggatgctgct
  61 ggcgctcctg gccctctccg cggcgcggcc atcggccagt gcagagtcac actggtgcta
 121 cgaggttcaa gccgagtcct ccaactaccc ctgcttggtg ccagtcaagt ggggtggaaa
 181 ctgccagaag gaccgccagt ccccccatcaa catcgtcacc accaaggcaa aggtggacaa
 241 aaaactggga cgcttcttct tctctggcta cgataagaag caaacgtgga ctgtccaaaa
 301 taacgggcac tcagtgatga tgttgctgga gaacaaggcc agcatttctg gaggaggact
 361 gcctgcccca taccaggcca aacagttgca cctgcactgg tccgacttgc catataaggg
 421 ctcggagcac agcctcgatg gggagcactt tgccatggag atgcacatag tacatgagaa
 481 agagaagggg acatcgagga atgtgaaaga ggcccaggac cctgaagacg aaattgcggt
 541 gctggccttt ctggtggagg ctggaaccca ggtgaacgag ggcttccagc cactggtgga
 601 ggcactgtct aatatcccca aacctgagat gagcactacg atggcagaga gcagcctgtt
 661 ggacctgctc cccaaggagg agaaactgag gcactacttc cgctacctgg gctcactcac
 721 cacaccgacc tgcgatgaga aggtcgtctg gactgtgttc cgggagccca ttcagcttca
 781 cagagaacag atcctggcat tctctcagaa gctgtactac gacaaggaac agacagtgag
 841 catgaaggac aatgtcaggc ccctgcagca gctggggcag cgcacggtga taaagtccgg
 901 ggccccgggt cggccgctgc cctgggccct gcctgccctg ctgggcccca tgctggcctg
 961 cctgctggcc ggcttcctgc gatgatggct cacttctgca cgcagcctct ctgttgcctc
1021 agctctccaa gttccaggct tccggtcctt agccttccca ggtgggactt taggcatgat
1081 taaaatatgg acatattttt ggag (SEQ ID NO:25)
```

FIGURE 16A

CAH4 (carbonic anhydrase iv precursor, NM_000717)

```
RMLLALLALSAARPSASAESHWCYEVQAESSNYPCLVPVKWGG
CQKDRQSPINIVTTKAKVDKKLGRFFFSGYDKKQTWTVQNNGHSVMMLLENKASISG
GLPAPYQAKQLHLHWSDLPYKGSEHSLDGEHFAMEMHIVHEKEKGTSRNVKEAQDPE
EIAVLAFLVEAGTQVNEGFQPLVEALSNIPKPEMSTTMAESSLLDLLPKEEKLRHYF
YLGSLTTPTCDEKVVWTVFREPIQLHREQILAFSQKLYYDKEQTVSMKDNVRPLQQL
QRTVIKSGAPGRPLPWALPALLGPMLACLLAGFLR (SEQ ID NO:26)
```

FIGURE 16B

PA21 (phopholipase a2 precursor, NM_000928)

```
   1 tggtcatctc agttcttttc tcaccttgac tgcaagatga aactccttgt gctagctgtg
  61 ctgctcacag tggccgccgc cgacagcggc atcagccctc gggccgtgtg gcagttccgc
 121 aaaatgatca agtgcgtgat cccggggagt gaccccttct tggaatacaa caactacggc
 181 tgctactgtg gcttgggggg ctcaggcacc cccgtggatg aactggacaa gtgctgccag
 241 acacatgaca actgctatga ccaggccaag aagctggaca gctgtaaatt tctgctggac
 301 aacccgtaca cccacaccta ttcatactcg tgctctggct cggcaatcac ctgtagcagc
 361 aaaaacaaag agtgtgaggc cttcatttgc aactgcgacc gcaacgctgc catctgcttt
 421 tcaaaagctc catataacaa ggcacacaag aacctggaca ccaagaagta ttgtcagagt
 481 tgaatatcac ctctcaaaag catcacctct atctgcctca tctcacactg tactctccaa
 541 taaagcacct tgttgaaaga cctcaaaaaa aaaaaaaaaa aaaaa (SEQ ID NO:27)
```

FIGURE 17A

PA21 (phopholipase a2 precursor, NM_000928)

```
KLLVLAVLLTVAAADSGISPRAVWQFRKMIKCVIPGSDPFLEY
NYGCYCGLGGSGTPVDELDKCCQTHDNCYDQAKKLDSCKFLLDNPYTHTYSYSCSGS
ITCSSKNKECEAFICNCDRNAAICFSKAPYNKAHKNLDTKKYCQS (SEQ ID NO:28)
```

FIGURE 17B

PAR2 (proteinase activated receptor 2 precursor, NM_005242)

```
   1 tgaaacctaa cccgccctgg ggaggcgcgc agcagaggct ccgattcggg gcaggtgaga
  61 ggctgacttt ctctcggtgc gtccagtgga gctctgagtt tcgaatcggc ggcggcggat
 121 tccccgcgcg cccggcgtcg gggcttccag gaggatgcgg agccccagcg cggcgtggct
 181 gctgggggcc gccatcctgc tagcagcctc tctctcctgc agtggcacca tccaaggaac
 241 caatagatcc tctaaaggaa gaagccttat tggtaaggtt gatggcacat cccacgtcac
 301 tggaaaagga gttacagttg aaacagtctt ttctgtggat gagttttctg catctgtcct
 361 cactggaaaa ctgaccactg tcttccttcc aattgtctac acaattgtgt ttgtggtggg
 421 tttgccaagt aacggcatgg ccctgtgggt ctttcttttc cgaactaaga agaagcaccc
 481 tgctgtgatt tacatggcca atctggcctt ggctgacctc ctctctgtca tctggttccc
 541 cttgaagatt gcctatcaca tacatggcaa caactggatt tatggggaag ctctttgtaa
 601 tgtgcttatt ggctttttct atggcaacat gtactgttcc attctcttca tgacctgcct
 661 cagtgtgcag aggtattggg tcatcgtgaa ccccatgggg cactccagga agaaggcaaa
 721 cattgccatt ggcatctccc tggcaatatg gctgctgatt ctgctggtca ccatcccttt
 781 gtatgtcgtg aagcagacca tcttcattcc tgccctgaac atcacgacct gtcatgatgt
 841 tttgcctgag cagctcttgg tgggagacat gttcaattac ttcctctctc tggccattgg
 901 ggtctttctg ttcccagcct tcctcacagc ctctgcctat gtgctgatga tcagaatgct
 961 gcgatcttct gccatggatg aaaactcaga gaagaaaagg aagagggcca tcaaactcat
1021 tgtcactgtc ctggccatgt acctgatctg cttcactcct agtaaccttc tgcttgtggt
1081 gcattatttt ctgattaaga gccagggcca gagccatgtc tatgccctgt acattgtagc
1141 cctctgcctc tctaccctta acagctgcat cgaccccttt gtctattact ttgtttcaca
1201 tgatttcagg gatcatgcaa agaacgctct cctttgccga agtgtccgca ctgtaaagca
1261 gatgcaagta tccctcacct caaagaaaca ctccaggaaa tccagctctt actcttcaag
1321 ttcaaccact gttaagacct cctattgagt tttccaggtc ctcagatggg aattgcacag
1381 taggatgtgg aacctgttta atgttatgag gacgtgtctg ttatttccta atcaaaaagg
1441 tctcaccaca taccatgtgg atgcagcacc tctcaggatt gctaggagct cccctgtttg
1501 catgagaaaa gtagtccccc aaattaacat cagtgtctgt ttcagaatct ctctactcag
1561 atgaccccag aaactgaacc aacagaagca gacttttcag aagatggtga agacagaaac
1621 ccagtaactt gcaaaaagta gacttggtgt gaagactcac ttctcagctg aaattatata
1681 tatacacata tatatatttt acatctggga tcatgataga cttgttaggg cttcaaggcc
1741 ctcagagatg atcagtccaa ctgaacgacc ttacaaatga ggaaaccaag ataaatgagc
1801 tgccagaatc aggtttccaa tcaacagcag tgagttggga ttggacagta gaatttcaat
1861 gtccagtgag tgaggttctt gtaccacttc atcaaaatca tggatcttgg ctgggtgcgg
1921 tgcctcatgc ctgtaatcct agcactttgg gaggctgagg caggcaatca cttgaggtca
1981 ggagttcgag accagcctgg ccatcatggc gaaacctcat ctctactaaa aatacaaaag
2041 ttaaccaggt gtgtggtgca cgtttgtaat cccagttact caggaggctg aggcacaaga
2101 attgagtatc actttaactc aggaggcaga ggttgcagtg agccgagatt gcaccactgc
2161 actccagctt gggtgataaa ataaaataaa atagtcgtga atcttgttca aaatgcagat
2221 tcctcagatt caataatgag agctcagact gggaacaggg cccaggaatc tgtgtggtac
2281 aaacctgcat ggtgtttatg cacacagaga tttgagaacc attgttctga atgctgcttc
2341 catttgacaa agtgccgtga taatttttga aaagagaagc aaacaatggt gtctctttta
2401 tgttcagctt ataatgaaat ctgtttgttg acttattagg actttgaatt atttctttat
2461 taaccctctg agtttttgta tgtattatta ttaaagaaaa atgcaatcag gattttaaac
2521 atgtaaatac aaatttttga taacttttga tgacttcagt gaaattttca ggtagtctga
2581 gtaatagatt gttttgccac ttagaatagc atttgccact tagtatttta aaaaataatt
2641 gttggagtat ttattgtcag ttttgttcac ttgttatcta atacaaaatt ataaagcctt
2701 cagagggttt ggaccacatc tctttggaaa atagtttgca acatatttaa gagatacttg
2761 atgccaaaat gactttatac aacgattgta tttgtgactt ttaaaaataa ttattttatt
2821 gtgtaattga tttataaata acaaaatttt ttttacaact taaaaaaaaa aaaaaa (SEQ
ID NO:29)
```

FIGURE 18A

PAR2 (proteinase activated receptor 2 precursor, NM_005242)

RSPSAAWLLGAAILLAASLSCSGTIQGTNRSSKGRSLIGKVDG
SHVTGKGVTVETVFSVDEFSASVLTGKLTTVFLPIVYTIVFVVGLPSNGMALWVFLF
TKKKHPAVIYMANLALADLLSVIWFPLKIAYHIHGNNWIYGEALCNVLIGFFYGNMY
SILFMTCLSVQRYWVIVNPMGHSRKKANIAIGISLAIWLLILLVTIPLYVVKQTIFI
ALNITTCHDVLPEQLLVGDMFNYFLSLAIGVFLFPAFLTASAYVLMIRMLRSSAMDE
SEKKRKRAIKLIVTVLAMYLICFTPSNLLLVVHYFLIKSQGQSHVYALYIVALCLST
NSCIDPFVYYFVSHDFRDHAKNALLCRSVRTVKQMQVSLTSKKHSRKSSSYSSSSTT
KTSY (SEQ ID NO:30)

FIGURE 18B

IDE (insulin-degrading enzyme, NM_004969)

```
   1 ccggctcgaa gcgcaacgag gaagcgtttg cggtgatccc ggcgactgcg ctggctaatg
  61 cggtaccggc tagcgtggct tctgcacccc gcactgccca gcaccttccg ctcagtcctc
 121 ggcgcccgcc tgccgcctcc ggagcgcctg tgtggtttcc aaaaaaagac ttacagcaaa
 181 atgaataatc cagccatcaa gagaatagga aatcacatta ccaagtctcc tgaagacaag
 241 cgagaatatc gagggctaga gctggccaat ggtatcaaag tacttcttat gagtgatccc
 301 accacggata agtcatcagc agcacttgat gtgcacatag gttcattgtc ggatcctcca
 361 aatattgctg gcttaagtca tttttgtgaa catatgcttt ttttgggaac aaagaaatac
 421 cctaaagaaa atgaatacag ccagtttctc agtgagcatg caggaagttc aaatgccttt
 481 actagtggag agcataccaa ttactatttt gatgtttctc atgaacacct agaaggtgcc
 541 ctagacaggt ttgcacagtt ttttctgtgc cccttgttcg atgaaagttg caaagacaga
 601 gaggtgaatg cagttgattc agaacatgag aagaatgtga tgaatgatgc ctggagactc
 661 tttcaattgg aaaaagctac agggaatcct aaacacccct tcagtaaatt tgggacaggt
 721 aacaaatata ctctggagac tagaccaaac caagaaggca ttgatgtaag acaagagcta
 781 ctgaaattcc attctgctta ctattcatcc aacttaatgg ctgtttgtgt tttaggtcga
 841 gaatctttag atgacttgac taatctggtg gtaaagttat tttctgaagt agagaacaaa
 901 aatgttccat tgccagaatt tcctgaacac cctttccaag aagaacatct taaacaactt
 961 tacaaaatag tacccattaa agatattagg aatctctatg tgacatttcc catacctgac
1021 cttcagaaat actacaaatc aaatcctggt cattatcttg gtcatctcat tgggcatgaa
1081 ggtcctggaa gtctgttatc agaacttaag tcaaagggct gggttaatac tcttgttggt
1141 gggcagaagg aaggagcccg aggttttatg ttttttatca ttaatgtgga cttgaccgag
1201 gaaggattat tacatgttga agatataatt ttgcacatgt ttcaatacat tcagaagtta
1261 cgtgcagaag gacctcaaga atgggttttc caagagtgca aggacttgaa tgctgttgct
1321 tttaggttta aagacaaaga gaggccacgg ggctatacat ctaagattgc aggaatattg
1381 cattattatc ccctagaaga ggtgctcaca gcggaatatt tactggaaga atttagacct
1441 gacttaatag agatggttct cgataaactc agaccagaaa atgtccgggt tgccatagtt
1501 tctaaatctt ttgaaggaaa aactgatcgc acagaagagt ggtatggaac ccagtacaaa
1561 caagaagcta taccggatga agtcatcaag aaatggcaaa atgctgacct gaatgggaaa
1621 tttaaacttc ctacaaagaa tgaatttatt cctacgaatt ttgagatttt accgttagaa
1681 aaagaggcga caccataccc tgctcttatt aaggatacag tcatgagcaa actttggttc
1741 aaacaagatg ataagaaaaa aaagccgaag gcttgtctca actttgaatt tttcagccca
1801 tttgcttatg tggacccctt gcactgtaac atggcctatt tgtaccttga gctcctcaaa
1861 gactcactca acgagtatgc atatgcagca gagctagcag gcttgagcta tgatctccaa
1921 aataccatct atgggatgta tctttcagtg aaaggttaca atgacaagca gccaatttta
1981 ctaaagaaga ttattgagaa aatggctacc tttgagattg atgaaaaaag atttgaaatt
2041 atcaaagaag catatatgcg atctcttaac aatttccggg ctgaacagcc tcaccagcat
2101 gccatgtact acctccgctt gctgatgact gaagtggcct ggactaaaga tgagttaaaa
2161 gaagctctgg atgatgtaac ccttcctcgc cttaaggcct tcatacctca gctcctgtca
2221 cggctgcaca ttgaagccct tctccatgga aacataacaa agcaggctgc attaggaatt
2281 atgcagatgg ttgaagacac cctcattgaa catgctcata ccaaacctct ccttccaagt
2341 cagctggttc ggtatagaga agttcagctc cctgacagag gatggtttgt ttatcagcag
2401 agaaatgaag ttcacaataa ctgtggcatc gagatatact accaaacaga catgcaaagc
2461 acctcagaga atatgtttct ggagctcttc tgtcagatta tctcggaacc ttgcttcaac
2521 accctgcgca ccaaggagca gttgggctat atcgtcttca gcgggccacg tcgagctaat
2581 ggcatacaga gcttgagatt catcatccag tcagaaaagc cacctcacta cctagaaagc
2641 agagtggaag ctttcttaat taccatggaa aagtccatag aggacatgac agaagaggcc
2701 ttccaaaaac acattcaggc attagcaatt cgtcgactag acaaaccaaa gaagctatct
2761 gctgagtgtg ctaaatactg gggagaaatc atctcccagc aatataattt tgacagagat
2821 aacactgagg ttgcatattt aaagacactt accaaggaag atatcatcaa attctacaag
2881 gaaatgttgg cagtagatgc tccaaggaga cataaggtat ccgtccatgt tcttgccagg
2941 gaaatggatt cttgtcctgt tgttggagag ttcccatgtc aaaatgacat aaatttgtca
3001 caagcaccag ccttgccaca acctgaagtg attcagaaca tgaccgaatt caagcgtggt
3061 ctgccactgt ttccccttgt gaaaccacat attaacttca tggctgcaaa actctgaaga
3121 ttccccatgc atgggaaagt gcaagtggat gcattcctga gtcttccaga gcctaagaaa
3181 atcatcttgg ccactttaat agtttctgat tcactattag agaaacaaac aaaaaattgt
3241 caaatgtcat tatgtagaaa tattataaat ccaaagtaa (SEQ ID NO:31)
```

FIGURE 19A

IDE (insulin-degrading enzyme, NM_004969)

MRYRLAWLLHPALPSTFRSVLGARLPPPERLCGFQKKTYSKMNN
PAIKRIGNHITKSPEDKREYRGLELANGIKVLLMSDPTTDKSSAALDVHIGSLSDPPN
IAGLSHFCEHMLFLGTKKYPKENEYSQFLSEHAGSSNAFTSGEHTNYYFDVSHEHLEG
ALDRFAQFFLCPLFDESCKDREVNAVDSEHEKNVMNDAWRLFQLEKATGNPKHPFSKF
GTGNKYTLETRPNQEGIDVRQELLKFHSAYYSSNLMAVCVLGRESLDDLTNLVVKLFS
EVENKNVPLPEFPEHPFQEEHLKQLYKIVPIKDIRNLYVTFPIPDLQKYYKSNPGHYL
GHLIGHEGPGSLLSELKSKGWVNTLVGGQKEGARGFMFFIINVDLTEEGLLHVEDIIL
HMFQYIQKLRAEGPQEWVFQECKDLNAVAFRFKDKERPRGYTSKIAGILHYYPLEEVL
TAEYLLEEFRPDLIEMVLDKLRPENVRVAIVSKSFEGKTDRTEEWYGTQYKQEAIPDE
VIKKWQNADLNGKFKLPTKNEFIPTNFEILPLEKEATPYPALIKDTVMSKLWFKQDDK
KKKPKACLNFEFFSPFAYVDPLHCNMAYLYLELLKDSLNEYAYAAELAGLSYDLQNTI
YGMYLSVKGYNDKQPILLKKIIEKMATFEIDEKRFEIIKEAYMRSLNNFRAEQPHQHA
MYYLRLLMTEVAWTKDELKEALDDVTLPRLKAFIPQLLSRLHIEALLHGNITKQAALG
IMQMVEDTLIEHAHTKPLLPSQLVRYREVQLPDRGWFVYQQRNEVHNNCGIEIYYQTD
MQSTSENMFLELFCQIISEPCFNTLRTKEQLGYIVFSGPRRANGIQSLRFIIQSEKPP
HYLESRVEAFLITMEKSIEDMTEEAFQKHIQALAIRRLDKPKKLSAECAKYWGEIISQ
QYNFDRDNTEVAYLKTLTKEDIIKFYKEMLAVDAPRRHKVSVHVLAREMDSCPVVGEF
PCQNDINLSQAPALPQPEVIQNMTEFKRGLPLFPLVKPHINFMAAKL (SEQ ID NO:32)

FIGURE 19B

MYO1A (myosin-1A, NM_005379)

```
   1 cagggagcct gggctggaag aggcagcaaa agggaaaatc agaagagtgg acactggcaa
  61 gaggagggca gccttttcc cagcttcctt gcaccatgga cagctcccat taagccacct
 121 ctccatcctg gggccaggac tcttatgccc cattcctgtc aaattgagat ttcatccacc
 181 attctccaag gacagtgaag ttatacccta gttccagtgt tgggatcagt ggccccctctg
 241 gacatgcctc tcctggaagg ttctgtgggg gtggaggatc ttgtcctcct ggaacccttg
 301 gtggaggagt cactgctcaa gaatcttcag cttcgctatg aaaacaagga gatttatacc
 361 tacattggga atgtggtgat ctcagtgaat ccctatcaac agcttcccat ctatgggcca
 421 gagttcattg ccaaatatca agactatact ttctatgagc tgaagcccca tatctacgca
 481 ttggcaaatg tggcgtacca gtcactgagg gacagggacc gagaccagtg tatcctcatc
 541 acaggcgaga gtggatcagg gaagactgag gccagcaagc tggtgatgtc ttatgtggct
 601 gccgtctgtg ggaaaggaga gcaggtgaac tctgtgaagg agcagctgct acagtctaac
 661 ccagtgctgg aggcttttgg caatgccaag accattcgca acaacaattc ctcccgattt
 721 ggaaaataca tggatattga atttgacttc aagggatccc ccctcggtgg tgtcatcaca
 781 aactatctgc ttgagaaatc ccgattagtg aagcagctca aaggagaaag gaacttccac
 841 atcttctatc agctgctggc tggagcagat gaacagctgc tgaaggccct gaagcttgag
 901 cgggatacaa ctggctatgc ctatctgaat catgaagtat ccagagtgga tggcatggac
 961 gacgcctcca gcttcagggc tgtacagagt gcaatggcag tgattgggtt ctcggaggag
1021 gagattcgac aagtgctaga ggtgacatcc atggtgctaa agctggggaa cgtgttggtg
1081 gctgatgagt tccaggccag tgggatacca gcaagtggca tccgtgatgg gagaggtgtt
1141 cgggagattg gggagatggt gggcttgaat tcagaagaag tagagagagc tttgtgctcg
1201 aggaccatgg aaacagccaa ggaaaaggtg gtcactgcac tgaatgttat gcaggctcag
1261 tatgctcggg acgccctggc taagaacatc tacagccgcc tctttgactg gatagtgaat
1321 cgaatcaatg agagcatcaa ggtgggcatc ggggaaaaga agaaggtaat gggagtcctt
1381 gatatctacg gttttgagat attagaggat aatagctttg agcaatttgt gatcaactac
1441 tgcaatgaga agctgcagca ggtgttcata gagatgaccc tgaaagaaga gcaagaggaa
1501 tataagagag aaggcatacc gtggacaaag gtggactact ttgataatgg catcatttgt
1561 aagctcattg agcataatca gcgaggtatc ctggccatgt tggatgagga gtgcctgcgg
1621 cctggggtgg tcagtgactc cactttccta gcaaagctga accagctctt ctccaagcat
1681 ggccactacg agagcaaagt cacccagaat gcccagcgtc agtatgacca caccatgggc
1741 ctcagctgct tccgcatctg ccactatgcg ggcaaggtga catacaacgt gaccagcttt
1801 attgacaaga ataatgacct actcttccga gacctgttgc aggccatgtg gaaggcccag
1861 caccccctcc ttcggtcctt gtttcctgag ggcaatccta agcaggcatc tctcaaacgc
1921 cccccgactg ctggggccca gttcaagagt tctgtggcca tcctcatgaa gaatctgtat
1981 tccaagagcc ccaactacat caggtgcata aagcccaatg agcatcagca gcgaggtcag
2041 ttctcttcag acctggtggc aacccaggct cggtacctgg gactgctgga gaacgtacgg
2101 gtgcgacggg caggctatgc ccaccgccag ggttatgggc ccttcctgga aaggtaccga
2161 ttgctgagcc ggagcacctg gcctcactgg aatgggggag accgggaagg tgttgagaag
2221 gtcctggggg agctgagcat gtcctcgggg gagctggcct ttggcaagac aaagatcttc
2281 attagaagcc ccaagactct tttctacctc gaagaacaga ggcgcctgag actccagcag
2341 ctggccacac tcatacagaa gatttaccga ggctggcgct gccgcaccca ctaccaactg
2401 atgcgaaaga gtcagatcct catctcctct tggtttcggg gaaacatgca aaagaaatgc
2461 tatgggaaga taaaggcatc cgtgttattg atccaggctt ttgtgagagg gtggaaggcc
2521 cgaaagaatt atcgcaaata tttccggtca gaggctgccc tcaccttggc agatttcatc
2581 tacaagagca tggtacagaa attcctactg gggctgaaga acaatttgcc atccacaaac
2641 gtcttagaca agacatggcc agccgccccc tacaagtgcc tcagcacagc aaatcaggag
2701 ctgcagcagc tcttctacca gtggaagtgc aagaggttcc gggatcagct gtccccgaag
2761 caggtagaga tcctgaggga aaagctctgt gccagtgaac tgttcaaggg caagaaggct
2821 tcatatcccc agagtgtccc cattccattc tgtggtgact acattgggct gcaagggaac
2881 cccaagctgc agaagctgaa aggcggggag gaggggcctg ttctgatggc agaggccgtg
2941 aagaaggtca atcgtggcaa tggcaagact tcttctcgga ttctcctcct gaccaagggc
3001 catgtgattc tcacagacac caagaagtcc caggccaaaa ttgtcattgg gctagacaat
3061 gtggctgggg tgtcagtcac cagcctcaag gatgggctct ttagcttgca tctgagtgag
3121 atgtcatcgg tgggctccaa gggggacttc ctgctggtca gcgagcatgt gattgaactg
3181 ctgaccaaaa tgtaccgggc tgtgctggat gccacgcaga ggcagcttac agtcaccgtg
```

FIGURE 20A

```
3241 actgagaagt tctcagtgag gttcaaggag aacagtgtgg ctgtcaaggt cgtccagggc
3301 cctgcaggtg gtgacaacag caagctacgc tacaaaaaaa aggggagtca ttgcttggag
3361 gtgactgtgc agtgaggagg gggcaccatg cagagatggc agttgcttcc tcctgaacca
3421 gcactaatcc ccctctgccc tcctgtgtgg gaggatctct aacccctctg atcgtggcgc
3481 atggcttggg gattaaacta cccttgaaga ggacccttgt cccaaaccct tcttgttctc
3541 tcctccaaaa gtagcttcct ccaacccgca gcctctctgc acactaataa aacatgtggc
3601 ttggaaaggt tcaaaaaaaa aaaa (SEQ ID NO:33)
```

FIGURE 20B

MYO1A (myosin-1A, NM_005379)

PLLEGSVGVEDLVLLEPLVEESLLKNLQLRYENKEIYTYIGNV
ISVNPYQQLPIYGPEFIAKYQDYTFYELKPHIYALANVAYQSLRDRDRDQCILITGE
GSGKTEASKLVMSYVAAVCGKGEQVNSVKEQLLQSNPVLEAFGNAKTIRNNNSSRFG
YMDIEFDFKGSPLGGVITNYLLEKSRLVKQLKGERNFHIFYQLLAGADEQLLKALKL
RDTTGYAYLNHEVSRVDGMDDASSFRAVQSAMAVIGFSEEEIRQVLEVTSMVLKLGN
LVADEFQASGIPASGIRDGRGVREIGEMVGLNSEEVERALCSRTMETAKEKVVTALN
MQAQYARDALAKNIYSRLFDWIVNRINESIKVGIGEKKKVMGVLDIYGFEILEDNSF
QFVINYCNEKLQQVFIEMTLKEEQEEYKREGIPWTKVDYFDNGIICKLIEHNQRGIL
MLDEECLRPGVVSDSTFLAKLNQLFSKHGHYESKVTQNAQRQYDHTMGLSCFRICHY
GKVTYNVTSFIDKNNDLLFRDLLQAMWKAQHPLLRSLFPEGNPKQASLKRPPTAGAQ
KSSVAILMKNLYSKSPNYIRCIKPNEHQQRGQFSSDLVATQARYLGLLENVRVRRAG
AHRQGYGPFLERYRLLSRSTWPHWNGGDREGVEKVLGELSMSSGELAFGKTKIFIRS
KTLFYLEEQRRLRLQQLATLIQKIYRGWRCRTHYQLMRKSQILISSWFRGNMQKKCY
KIKASVLLIQAFVRGWKARKNYRKYFRSEAALTLADFIYKSMVQKFLLGLKNNLPST
VLDKTWPAAPYKCLSTANQELQQLFYQWKCKRFRDQLSPKQVEILREKLCASELFKG
KASYPQSVPIPFCGDYIGLQGNPKLQKLKGGEEGPVLMAEAVKKVNRGNGKTSSRIL
LTKGHVILTDTKKSQAKIVIGLDNVAGVSVTSLKDGLFSLHLSEMSSVGSKGDFLLV
EHVIELLTKMYRAVLDATQRQLTVTVTEKFSVRFKENSVAVKVVQGPAGGDNSKLRY
KKGSHCLEVTVQ (SEQ ID NO:34)

FIGURE 20C

CYP2J2 (cytochrome P450 monooxygenase, NM_000775)

```
   1 gagccatgct cgcggcgatg ggctctctgg cggctgccct ctgggcagtg gtccatcctc
  61 ggactctcct actgggcact gtcgcctttc tgctcgctgc tgactttctc aaaagacggc
 121 gcccaaagaa ctacccgccg gggccctggc gcctgccctt ccttggcaac ttcttccttg
 181 tggacttcga gcagtcgcac ctggaggttc agctgtttgt gaagaaatat gggaaccttt
 241 ttagcttgga gcttggtgac atatctgcag ttcttattac tggcttgccc ttaatcaaag
 301 aagcccttat ccacatggac caaaactttg ggaaccgccc cgtgacccct atgcgagaac
 361 atatctttaa gaaaaatgga ttgattatgt caagtggcca ggcatggaag gagcaaagaa
 421 ggttcactct gacagcacta aggaactttg gtttaggaaa gaagagctta gaggaacgca
 481 ttcaggagga ggcccaacac ctcactgaag caataaaaga ggagaacgga cagccttttg
 541 accctcattt caagatcaac aatgcagttt ccaatatcat ttgctccatc accttcggag
 601 aacgctttga gtaccaggat agttggtttc agcagctgct gaagttacta gatgaagtca
 661 catacttgga ggcttcaaag acatgccagc tctacaatgt ctttccatgg ataatgaaat
 721 tcctgcctgg accccaccaa actctcttca gcaactggaa aaaactgaaa ttgtttgttt
 781 ctcatatgat tgacaaacac agaaaggatt ggaatcctgc agaaacaaga gactttattg
 841 atgcttacct taaagaaatg tcaaagcaca caggcaatcc tacttcaagt ttccatgaag
 901 aaaacctcat ctgcagcacc ctggacctct tctttgccgg aaccgagaca acttccacaa
 961 ctctgcgatg ggctctgctt tatatggccc tctacccaga aatccaagaa aaagtacaag
1021 ctgagattga cagagtgatt ggccaggggc agcagccgag cacagccgcc cgggagtcca
1081 tgccctacac caatgctgtc atccatgagg tgcagagaat gggcaacatc atccccctga
1141 acgttcccag ggaagtgaca gttgatacca ctttggctgg gtaccacctg cccaagggta
1201 ccatgatcct gaccaatttg acggcgctgc acagggaccc cacagagtgg gccacccctg
1261 acacattcaa tccggaccat tttctggaga atggacagtt taagaaaagg gaagccttta
1321 tgcctttctc aataggaaag cgggcatgcc tcggagaaca gttggccagg actgagctgt
1381 ttattttctt cacttccctt atgcaaaaat ttaccttcag gcccccaaac aatgagaagc
1441 tgagcctgaa gtttagaatg ggtatcacca tttccccagt cagtcaccgc ctctgcgctg
1501 ttcctcaggt gtaatattgt taagaaagaa aggggcaagg aaagtaagaa gacatggcac
1561 gtgttctgaa accactggtg tctgctcaga tgtgttggga caaaatgaaa gtgactttca
1621 agaaagatca gaggaatttg actcagagaa aactagatcc aaatcccagc tctactgtct
1681 cgtccgaatt agccttggga aaatcattta tatgctaaat aatttacctt tttatctagg
1741 agatgaaaag aggataatgt ttccttccat aaagaaagtt cttgtaagaa tcaaaagaaa
1801 tggtgagctt taagtggttt gtaaaccata aaacacatca taaaagttct atctataaaa
1861 aaaaaaaaaa aaaaaa (SEQ ID NO:35)
```

FIGURE 21A

CYP2J2 (cytochrome P450 monooxygenase, NM_000775)

```
LAAMGSLAAALWAVVHPRTLLLGTVAFLLAADFLKRRRPKNYP
PGPWRLPFLGNFFLVDFEQSHLEVQLFVKKYGNLFSLELGDISAVLITGLPLIKEALI
HMDQNFGNRPVTPMREHIFKKNGLIMSSGQAWKEQRRFTLTALRNFGLGKKSLEERIQ
EEAQHLTEAIKEENGQPFDPHFKINNAVSNIICSITFGERFEYQDSWFQQLLKLLDEV
TYLEASKTCQLYNVFPWIMKFLPGPHQTLFSNWKKLKLFVSHMIDKHRKDWNPAETRD
FIDAYLKEMSKHTGNPTSSFHEENLICSTLDLFFAGTETTSTTLRWALLYMALYPEIQ
EKVQAEIDRVIGQGQQPSTAARESMPYTNAVIHEVQRMGNIIPLNVPREVTVDTTLAG
YHLPKGTMILTNLTALHRDPTEWATPDTFNPDHFLENGQFKKREAFMPFSIGKRACLG
EQLARTELFIFFTSLMQKFTFRPPNNEKLSLKFRMGITISPVSHRLCAVPQV (SEQ ID
NO:36)
```

FIGURE 21B

PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214)

```
   1 gcccgctgcg gtaaatgggg cagaggccgg gaggggtggg ggttccccgc gccgcagcca
  61 tggagcagct tcgcgccgcc gcccgtctgc agattgttct gggccacctc ggccgccccc
 121 cggccggggc tgtcgtagct catcccactt cagggactat ttcctctgcc agtttccatc
 181 ctcaacaatt ccagtatact ctggataata atgttctaac cctggaacag agaaaatttt
 241 atgaagaaaa tgggtttcta gtaatcaaaa atcttgtacc tgatgccgat attcaacgct
 301 ttcggaatga gtttgaaaaa atctgcagaa aggaggtgaa accattagga ttaacagtaa
 361 tgagagatgt gaccatttcg aaatccgaat atgctccaag tgagaagatg atcacgaagg
 421 tccaggattt ccaggaagat aaggagctct tcagatactg cactctcccc gagattctga
 481 aatatgtgga gtgcttcact ggacctaata ttatggccat gcacacaatg ttgataaaca
 541 aacctccaga ttctggcaag aagacgtccc gtcacccctc gcaccaggac ctgcactatt
 601 tcccccttcag gcccagcgat ctcatcgttt gcgcctggac ggcgatggag cacatcagcc
 661 ggaacaacgg ctgtctggtt gtgctcccag gcacacacaa gggctccctg aagccccacg
 721 attaccccaa gtgggagggg ggagttaaca aaatgttcca cgggatccag gactacgagg
 781 aaaacaaggc ccgggtgcac ctggtgatgg agaagggcga cactgtttc ttccatcctt
 841 tgctcatcca cggatctggt cagaataaaa cccagggatt ccggaaggca atttcctgcc
 901 atttcgccag tgccgattgc cactacattg acgtgaaggg caccagtcaa gaaaacatcg
 961 agaaggaagt tgtaggaata gcacataaat tctttggagc tgaaaatagc gtgaacttga
1021 aggatatttg gatgtttcga gctcgacttg tgaaaggaga aagaaccaat ctttgaaata
1081 gccatctgct ataactcttt caacagaaaa ccaaaaccaa acgaaatgtc taaggaaaat
1141 gttttcttaa tgagatgatg taacctttc tatcacttgt taaaagcaga aaacatgtat
1201 caggtactta attgcataga gttagttttg cagcacaatg gtgttgcttt aatggaaaaa
1261 aaaaacagta aaagtgaaat attactgttt taaggaaaac taatttaggg tggcagccaa
1321 taaaggtggt tggtgtctaa tttaagtgtt aaatcaattt ctttcattca gttagctctt
1381 tacccaagaa gaagtgaatg atttggagct tagggtatgt tttgtatccc ctttctgata
1441 aacccattcc ctaccaattt tatgtcataa gagatttttt tcccccaaat ctagaacaat
1501 gtataataca ttcacatcta gtcaagggca taggaacggt gtcatggagt ccaaataaag
1561 tggatattcc tgctcgg (SEQ ID NO:37)
```

FIGURE 22A

PHYH (phytanoyl-CoA-hydroxylase (Refsum disease), NM_006214)

```
MEQLRAAARLQIVLGHLGRPSAGAVVAHPTSGTISSASFHPQQF
QYTLDNNVLTLEQRKFYEENGFLVIKNLVPDADIQRFRNEFEKICRKEVKPLGLTVMR
DVTISKSEYAPSEKMITKVQDFQEDKELFRYCTLPEILKYVECFTGPNIMAMHTMLIN
KPPDSGKKTSRHPLHQDLHYFPFRPSDLIVCAWTAMEHISRNNGCLVVLPGTHKGSLK
PHDYPKWEGGVNKMFHGIQDYEENKARVHLVMEKGDTVFFHPLLIHGSGQNKTQGFRK
AISCHFASADCHYIDVKGTSQENIEKEVVGIAHKFFGAENSVNLKDIWMFRARLVKGE
RTNL (SEQ ID NO:38)
```

FIGURE 22B

CYB5 (cytochrome b5, 3' end, NM_001914)

```
     1 atggcagagc agtcggacga ggccgtgaag tactacaccc tagaggagat tcagaagcac
    61 aaccacagca agagcacctg gctgatcctg caccacaagg tgtacgattt gaccaaattt
   121 ctggaagagc atcctggtgg ggaagaagtt ttaagggaac aagctggagg tgacgctact
   181 gagaactttg aggatgtcgg gcactctaca gatgccaggg aaatgtccaa aacattcatc
   241 attggggagc tccatccaga tgacagacca aagttaaaca agcctccaga accttaaagg
   301 cggtgtttca aggaaactct tatcactact attgattcta gttccagttg gtggaccaac
   361 tgggtgatcc ctgccatctc tgcagtggcc gtcgccttga tgtatcgcct atacatggca
   421 gaggactgaa cacctcctca gaagtcagcg caggaagagc ctgctttgga cacgggagaa
   481 aagaagccat tgctaactac ttcaactgac agaaaccttc acttgaaaac aatgatttta
   541 atatatctct ttctttttct tccgacatta gaaacaaaac aaaaagaact gtcctttctg
   601 cgctcaaatt tttcgagtgt gccttttttat tcatctactt tattttgatg tttccttaat
   661 gtgtaattta cttattataa gcatgatctt ttaaaaatat atttggcttt taaagt (SEQ
ID NO:39)
```

FIGURE 23A

CYB5 (cytochrome b5, 3' end, NM_001914)

```
MAEQSDEAVKYYTLEEIQKHNHSKSTWLILHHKVYDLTKFLEEH
PGGEEVLREQAGGDATENFEDVGHSTDAREMSKTFIIGELHPDDRPKLNKPPEP (SEQ ID
NO:40)
```

FIGURE 23B

COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863)

```
   1 cctcctggga gggagctgaa gccgctcgca agactcccgt agtccccacc tctctcagct
  61 tccggctggt agtagttccg cttcctgtcc gactgtggtg tctttgctga gggtcacatt
 121 gagctgcagg ttgaatccgg ggtgccttta ggattcagca ccatggcgga agacatggag
 181 accaaaatca agaactacaa gaccgccccc tttgacagcc gcttccccaa ccagaaccag
 241 actagaaact gctggcagaa ctacctggac ttccaccgct gtcagaaggc aatgaccgct
 301 aaaggaggcg atatctctgt gtgcgaatgg taccagcgtg tgtaccagtc cctctgcccc
 361 acatcctggg tcacagactg ggatgagcaa cgggctgaag gcacgtttcc cgggaagatc
 421 tgaactggct gcatctccct ttcctctgtc ctccatcctt ctcccaggat ggtgaagggg
 481 gacctggtac ccagtgatcc ccaccccagg atcctaaatc atgacttacc tgctaataaa
 541 aactcattgg aaaagtgaaa aaaaaaaaaa aaaaaaaa (SEQ ID NO:41)
```

FIGURE 24A

COXVIb (coxVIb gene, last exon and flanking sequence, NM_001863)

```
MAEDMETKIKNYKTAPFDSRFPNQNQTRNCWQNYLDFHRCQKAM
TAKGGDISVCEWYQRVYQSLCPTSWVTDWDEQRAEGTFPGKI (SEQ ID NO:42)
```

FIGURE 24B

TCF4 (NM_030756)

```
   1 ggtttttttt ttttaccccc ctttttttatt tattattttt ttgcacattg agcggatcct
  61 tgggaacgag agaaaaaaga aacccaaact cacgcgtgca gaagatctcc ccccccttcc
 121 cctcccctcc tccctctttt cccctcccca ggagaaaaag acccccaagc agaaaaaagt
 181 tcaccttgga ctcgtctttt tcttgcaata ttttttgggg gggcaaaact ttgagggggt
 241 gatttttttt ggcttttctt cctccttcat ttttcttcca aaattgctgc tggtgggtga
 301 aaaaaaaatg ccgcagctga acggcggtgg aggggatgac ctaggcgcca acgacgaact
 361 gatttccttc aaagacgagg gcgaacagga ggagaagagc tccgaaaact cctcggcaga
 421 gagggattta gctgatgtca aatcgtctct agtcaatgaa tcagaaacga atcaaaacag
 481 ctcctccgat tccgaggcgg aaagacggcc tccgcctcgc tccgaaagtt tccgagacaa
 541 atcccgggaa agtttggaag aagcggccaa gaggcaagat ggagggctct ttaaggggcc
 601 accgtatccc ggctacccct tcatcatgat ccccgacctg acgagcccct acctccccaa
 661 cggatcgctc tcgcccaccg cccgaaccta tctccagatg aaatggccac tgcttgatgt
 721 ccaggcaggg agcctccaga gtagacaagc cctcaaggat gcccggtccc catcaccggc
 781 acacattgtc tctaacaaag tgccagtggt gcagcaccct caccatgtcc acccctcac
 841 gcctcttatc acgtacagca atgaacactt cacgccggga aacccacctc cacacttacc
 901 agccgacgta gaccccaaaa caggaatccc acggcctccg caccctccag atatatcccc
 961 gtattaccca ctatcgcctg gcaccgtagg acaaatcccc catccgctag gatggttagt
1021 accacagcaa ggtcaaccag tgtacccaat cacgacagga ggattcagac acccctaccc
1081 cacagctctg accgtcaatg cttccgtgtc caggttccct ccccatatgg tcccaccaca
1141 tcatacgcta cacacgacgg gcattccgca tccggccata gtcacaccaa cagtcaaaca
1201 ggaatcgtcc cagagtgatg tcggctcact ccatagttca aagcatcagg actccaaaaa
1261 ggaagaagaa aagaagaagc cccacataaa gaaacctctt aatgcattca tgttgtatat
1321 gaaggaaatg agagcaaagg tcgtagctga gtgcacgttg aaagaaagcg cggccatcaa
1381 ccagatcctt gggcggaggt ggcatgcact gtccagagaa gagcaagcga aatactacga
1441 gctggcccgg aaggagcgac agcttcatat gcaactgtac cccggctggt ccgcgcggga
1501 taactatgga aagaagaaga agaggaaaag ggacaagcag ccgggagaga ccaatgaaca
1561 cagcgaatgt ttcctaaatc cttgcctttc acttcctccg attacagacc tcagcgctcc
1621 taagaaatgc cgagcgcgct ttggccttga tcaacagaat aactggtgcg gcccttgcag
1681 gagaaaaaaa aagtgcgttc gctacataca aggtgaaggc agctgcctca gcccaccctc
1741 ttcagatgga agcttactag attcgcctcc cccctccccg aacctgctag gctcccctcc
1801 ccgagacgcc aagtcacaga ctgagcagac ccagcctctg tcgctgtccc tgaagcccga
1861 ccccctggcc cacctgtcca tgatgcctcc gccacccgcc ctcctgctcg ctgaggccac
1921 ccacaaggcc tccgccctct gtcccaacgg ggccctggac ctgcccccag ccgctttgca
1981 gcctgccgcc ccctcctcat caattgcaca gccgtcgact tcttggttac attcccacag
2041 ctccctggcc gggacccagc cccagccgct gtcgctcgtc accaagtctt tagaatagct
2101 ttagcgtcgt gaaccccgct gctttgttta tggttttgtt tcacttttct taatttgccc
2161 cccacccccа ccttgaaagg ttttgttttg tactctctta attttgtgcc atgtggctac
2221 attagttgat gtttatcgag ttcattggtc aatatttgac ccattcttat ttcaatttct
2281 ccttttaaat atgtagatga gagaagaacc tcatgattgg taccaaaatt tttatcaaca
2341 gctgtttaaa gtctttgtag cgtttaaaaa atatatatat atacataact gttatgtagt
2401 tcggatagct tagttttaaa agactgatta aaaaacaaaa aaaa (SEQ ID NO:43)
```

FIGURE 25A

TCF4 (NM_030756)

MPQLNGGGGDDLGANDELISFKDEGEQEEKSSENSSAERDLADV
KSSLVNESETNQNSSSDSEAERRPPPRSESFRDKSRESLEEAAKRQDGGLFKGPPYPG
YPFIMIPDLTSPYLPNGSLSPTARTYLQMKWPLLDVQAGSLQSRQALKDARSPSPAHI
VSNKVPVVQHPHHVHPLTPLITYSNEHFTPGNPPPHLPADVDPKTGIPRPPHPPDISP
YYPLSPGTVGQIPHPLGWLVPQQGQPVYPITTGGFRHPYPTALTVNASVSRFPPHMVP
PHHTLHTTGIPHPAIVTPTVKQESSQSDVGSLHSSKHQDSKKEEEKKKPHIKKPLNAF
MLYMKEMRAKVVAECTLKESAAINQILGRRWHALSREEQAKYYELARKERQLHMQLYP
GWSARDNYGKKKKRKRDKQPGETNEHSECFLNPCLSLPPITDLSAPKKCRARFGLDQQ
NNWCGPCRRKKKCVRYIQGEGSCLSPPSSDGSLLDSPPPSPNLLGSPPRDAKSQTEQT
QPLSLSLKPDPLAHLSMMPPPPALLLAEATHKASALCPNGALDLPPAALQPAAPSSSI
AQPSTSWLHSHSSLAGTQPQPLSLVTKSLE (SEQ ID NO:44)

FIGURE 25B

CAD17 (liver-intestine cadherin, NM_004063)

```
   1 agggagtgtt cccgggggag atactccagt cgtagcaaga gtctcgacca ctgaatggaa
  61 gaaaaggact tttaaccacc attttgtgac ttacagaaag gaatttgaat aaagaaaact
 121 atgatacttc aggcccatct tcactccctg tgtcttctta tgctttattt ggcaactgga
 181 tatggccaag aggggaagtt tagtggaccc ctgaaaccca tgacattttc tatttatgaa
 241 ggccaagaac cgagtcaaat tatattccag tttaaggcca atcctcctgc tgtgactttt
 301 gaactaactg gggagacaga caacatattt gtgatagaac gggagggact tctgtattac
 361 aacagagcct tggacaggga aacaagatct actcacaatc tccaggttgc agccctggac
 421 gctaatggaa ttatagtgga gggtccagtc cctatcacca tagaagtgaa ggacatcaac
 481 gacaatcgac ccacgtttct ccagtcaaag tacgaaggct cagtaaggca gaactctcgc
 541 ccaggaaagc ccttcttgta tgtcaatgcc acagacctgg atgatccggc cactcccaat
 601 ggccagcttt attaccagat tgtcatccag cttcccatga tcaacaatgt catgtacttt
 661 cagatcaaca acaaaacggg agccatctct cttacccgag agggatctca ggaattgaat
 721 cctgctaaga atccttccta taatctggtg atctcagtga aggacatggg aggccagagt
 781 gagaattcct tcagtgatac cacatctgtg gatatcatag tgacagagaa tatttggaaa
 841 gcaccaaaac ctgtggagat ggtggaaaac tcaactgatc ctcaccccat caaaatcact
 901 caggtgcggt ggaatgatcc cggtgcacaa tattccttag ttgacaaaga gaagctgcca
 961 agattcccat tttcaattga ccaggaagga gatatttacg tgactcagcc cttggaccga
1021 gaagaaaagg atgcatatgt tttttatgca gttgcaaagg atgagtacgg aaaaccactt
1081 tcatatccgc tggaaattca tgtaaaagtt aaagatatta atgataatcc acctacatgt
1141 ccgtcaccag taaccgtatt tgaggtccag gagaatgaac gactgggtaa cagtatcggg
1201 acccttactg cacatgacag ggatgaagaa aatactgcca acagttttct aaactacagg
1261 attgtggagc aaactcccaa acttcccatg gatggactct tcctaatcca aacctatgct
1321 ggaatgttac agttagctaa acagtccttg aagaagcaag atactcctca gtacaactta
1381 acgatagagg tgtctgacaa agatttcaag acccttttgtt ttgtgcaaat caacgttatt
1441 gatatcaatg atcagatccc catctttgaa aaatcagatt atggaaacct gactcttgct
1501 gaagacacaa acattgggtc caccatctta accatccagg ccactgatgc tgatgagcca
1561 tttactggga gttctaaaat tctgtatcat atcataaagg gagacagtga gggacgcctg
1621 ggggttgaca cagatcccca taccaacacc ggatatgtca taattaaaaa gcctcttgat
1681 tttgaaacag cagctgtttc caacattgtg ttcaaagcag aaaatcctga gcctctagtg
1741 tttggtgtga agtacaatgc aagttctttt gccaagttca cgcttattgt gacagatgtg
1801 aatgaagcac ctcaattttc ccaacacgta ttccaagcga aagtcagtga ggatgtagct
1861 ataggcacta aagtgggcaa tgtgactgcc aaggatccag aaggtctgga cataagctat
1921 tcactgaggg gagacacaag aggttggctt aaaattgacc acgtgactgg tgagatcttt
1981 agtgtggctc cattggacag agaagccgga agtccatatc gggtacaagt ggtggccaca
2041 gaagtagggg ggtcttcctt gagctctgtg tcagagttcc acctgatcct tatggatgtg
2101 aatgacaacc ctcccaggct agccaaggac tacacgggct tgttcttctg ccatcccctc
2161 agtgcacctg gaagtctcat tttcgaggct actgatgatg atcagcactt atttcggggt
2221 ccccatttta cattttccct cggcagtgga agcttacaaa acgactggga agtttccaaa
2281 atcaatggta ctcatgcccg actgtctacc aggcacacag agtttgagga gagggagtat
2341 gtcgtcttga tccgcatcaa tgatgggggt cggccaccct tggaaggcat tgtttcttta
2401 ccagttacat tctgcagttg tgtggaagga agttgtttcc ggccagcagg tcaccagact
2461 gggataccca ctgtgggcat ggcagttggt atactgctga ccacccttct ggtgattggt
2521 ataattttag cagttgtgtt tatccgcata aagaaggata aaggcaaaga taatgttgaa
2581 agtgctcaag catctgaagt caaacctctg agaagctgaa tttgaaaagg aatgtttgaa
2641 tttatatagc aagtgctatt tcagcaacaa ccatctcatc ctattacttt tcatctaacg
2701 tgcattataa ttttttaaac agatattccc tcttgtcctt taatatttgc taaatatttc
2761 ttttttgagg tggagtcttg ctctgtcgcc caggctggag tacagtggtg tgatcccagc
2821 tcactgcaac ctccgcctcc tgggttcaca tgattctcct gcctcagctt cctaagtagc
2881 tgggtttaca ggcacccacc accatgccca gctaattttt gtatttttaa tagagacggg
2941 gtttcgccat ttggccaggc tggtcttgaa ctcctgacgt caagtgatct gcctgccttg
3001 gtctcccaat acaggcatga accactgcac ccacctactt agatatttca tgtgctatag
3061 acattagaga gatttttcat ttttccatga catttttcct ctctgcaaat ggcttagcta
```

FIGURE 26A

3121 cttgtgtttt tccctttggg ggcaagacag actcattaaa tattctgtac atttttttctt
3181 tatcaaggag atatatcagt gttgtctcat agaactgcct ggattccatt tatgtttttt
3241 ctgattccat cctgtgtccc cttcatcctt gactcctttg gtatttcact gaatttcaaa
3301 catttgtcag agaagaaaaa cgtgaggact caggaaaaat aaataaataa aagaacagcc
3361 ttttccctta gtattaacag aaatgtttct gtgtcattaa ccatctttaa tcaatgtgac
3421 atgttgctct ttggctgaaa ttcttcaact tggaaatgac acagacccac agaaggtgtt
3481 caaacacaac ctactctgca aaccttggta aaggaaccag tcagctggcc agatttcctc
3541 actacctgcc atgcatacat gctgcgcatg ttttcttcat tcgtatgtta gtaaagtttt
3601 ggttattata tatttaacat gtggaagaaa acaagacatg aaaagagtgg tgacaaatca
3661 agaataaaca ctggttgtag tcagttttgt ttgttaa (SEQ ID No:45)

FIGURE 26B

CAD17 (liver-intestine cadherin, NM_004063)

MILQAHLHSLCLLMLYLATGYGQEGKFSGPLKPMTFSIYEGQEP
SQIIFQFKANPPAVTFELTGETDNIFVIEREGLLYYNRALDRETRSTHNLQVAALDAN
GIIVEGPVPITIEVKDINDNRPTFLQSKYEGSVRQNSRPGKPFLYVNATDLDDPATPN
GQLYYQIVIQLPMINNVMYFQINNKTGAISLTREGSQELNPAKNPSYNLVISVKDMGG
QSENSFSDTTSVDIIVTENIWKAPKPVEMVENSTDPHPIKITQVRWNDPGAQYSLVDK
EKLPRFPFSIDQEGDIYVTQPLDREEKDAYVFYAVAKDEYGKPLSYPLEIHVKVKDIN
DNPPTCPSPVTVFEVQENERLGNSIGTLTAHDRDEENTANSFLNYRIVEQTPKLPMDG
LFLIQTYAGMLQLAKQSLKKQDTPQYNLTIEVSDKDFKTLCFVQINVIDINDQIPIFE
KSDYGNLTLAEDTNIGSTILTIQATDADEPFTGSSKILYHIIKGDSEGRLGVDTDPHT
NTGYVIIKKPLDFETAAVSNIVFKAENPEPLVFGVKYNASSFAKFTLIVTDVNEAPQF
SQHVFQAKVSEDVAIGTKVGNVTAKDPEGLDISYSLRGDTRGWLKIDHVTGEIFSVAP
LDREAGSPYRVQVVATEVGGSSLSSVSEFHLILMDVNDNPPRLAKDYTGLFFCHPLSA
PGSLIFEATDDDQHLFRGPHFTFSLGSGSLQNDWEVSKINGTHARLSTRHTEFEEREY
VVLIRINDGGRPPLEGIVSLPVTFCSCVEGSCFRPAGHQTGIPTVGMAVGILLTTLLV
IGIILAVVFIRIKKDKGKDNVESAQASEVKPLRS (SEQ ID NO:46)

FIGURE 26C

CLDN15 (claudin 15, NM_014343)

```
   1 ctcgtcaaca gctgccgcgc gcaggcttag ctcattcctc tgacctgcca ggaagcagag
  61 agacccacag agcaggaggg aggcagaaag tggagacgga cctgagcccg aggaagaggc
 121 aggcagaggc tgaggctgat tccaccccag cctgcctgga caaccctcct tagccgcagc
 181 cccttccagt tccctagggg ttctgccccc ccccctctct ggggcaccag ccccccaggg
 241 tcctgcatcc caccatgtcg atggctgtgg aaacctttgg cttcttcatg gcaactgtgg
 301 ggctgctgat gctgggggtg actctgccaa acagctactg gcgagtgtcc actgtgcacg
 361 ggaacgtcat caccaccaac accatcttcg agaacctctg gtttagctgt gccaccgact
 421 ccctgggcgt ctacaactgc tgggagttcc cgtccatgct ggccctctct gggtatattc
 481 aggcctgccg ggcactcatg atcaccgcca tcctcctggg cttcctcggc ctcttgctag
 541 gcatagcggg cctgcgctgc accaacattg ggggcctgga gctctccagg aaagccaagc
 601 tggcggccac cgcaggggcc ctccacattc tggccggtat ctgcgggatg gtggccatct
 661 cctggtacgc cttcaacatc acccgggact tcttcgaccc cttgtacccc ggaaccaagt
 721 acgagctggg ccccgccctc tacctggggt ggagcgcctc actgatctcc atcctgggtg
 781 gcctctgcct ctgctccgcc tgctgctgcg gctctgacga ggacccagcc gccagcgccc
 841 ggcggcccta ccaggctccc gtgtccgtga tgcccgtcgc cacctcggac caagaaggcg
 901 acagcagctt tggcaaatac ggcagaaacg cctacgtgta gcagctctgg cccgtgggcc
 961 ccgctgtctt cccactgccc caaggagagg ggacctggcc ggggcccatt cccctatagt
1021 aacctcaggg gccggccacg ccccgctccc gtagccccgc cccggccacg gccccgtgtc
1081 ttgcactctc atggcccctc caggccaaga actgctcttg ggaagtcgca tatctccact
1141 ctgaggctgg atccctcatc ttctgaccct gggttctggg ctgtgaaggg gacggtgtcc
1201 ccgcacgttt gtattgtgta taaatacatt cattaataaa tgcatattgt gaccgttc
```

(SEQ ID NO:47)

FIGURE 27A

CLDN15 (claudin 15, NM_014343)

MSMAVETFGFFMATVGLLMLGVTLPNSYWRVSTVHGNVITTNTI
FENLWFSCATDSLGVYNCWEFPSMLALSGYIQACRALMITAILLGFLGLLLGIAGLRC
TNIGGLELSRKAKLAATAGALHILAGICGMVAISWYAFNITRDFFDPLYPGTKYELGP
ALYLGWSASLISILGGLCLCSACCCGSDEDPAASARRPYQAPVSVMPVATSDQEGDSS
FGKYGRNAYV (SEQ ID NO:48)

FIGURE 27B

CFTR (chloride channel, NM_000492)

```
   1 aattggaagc aaatgacatc acagcaggtc agagaaaaag ggttgagcgg caggcaccca
  61 gagtagtagg tctttggcat taggagcttg agcccagacg gccctagcag ggaccccagc
 121 gcccgagaga ccatgcagag gtcgcctctg gaaaaggcca gcgttgtctc caaacttttt
 181 ttcagctgga ccagaccaat tttgaggaaa ggatacagac agcgcctgga attgtcagac
 241 atataccaaa tcccttctgt tgattctgct gacaatctat ctgaaaaatt ggaaagagaa
 301 tgggatagag agctggcttc aaagaaaaat cctaaactca ttaatgccct tcggcgatgt
 361 tttttctgga gatttatgtt ctatggaatc tttttatatt taggggaagt caccaaagca
 421 gtacagcctc tcttactggg aagaatcata gcttcctatg acccggataa caaggaggaa
 481 cgctctatcg cgatttatct aggcataggc ttatgccttc tctttattgt gaggcactg
 541 ctcctacacc cagccatttt tggccttcat cacattggaa tgcagatgag aatagctatg
 601 tttagtttga tttataagaa gactttaaag ctgtcaagcc gtgttctaga taaaataagt
 661 attggacaac ttgttagtct cctttccaac aacctgaaca aatttgatga aggacttgca
 721 ttggcacatt tcgtgtggat cgctcctttg caagtggcac tcctcatggg gctaatctgg
 781 gagttgttac aggcgtctgc cttctgtgga cttggtttcc tgatagtcct tgccctttt
 841 caggctgggc tagggagaat gatgatgaag tacagagatc agagagctgg gaagatcagt
 901 gaaagacttg tgattacctc agaaatgatt gaaaatatcc aatctgttaa ggcatactgc
 961 tgggaagaag caatggaaaa aatgattgaa aacttaagac aaacagaact gaaactgact
1021 cggaaggcag cctatgtgag atacttcaat agctcagcct tcttcttctc agggttcttt
1081 gtggtgtttt tatctgtgct tccctatgca ctaatcaaag gaatcatcct ccggaaaata
1141 ttcaccacca tctcattctg cattgttctg cgcatggcgg tcactcggca atttccctgg
1201 gctgtacaaa catggtatga ctctcttgga gcaataaaca aaatacagga tttcttacaa
1261 aagcaagaat ataagacatt ggaatataac ttaacgacta cagaagtagt gatggagaat
1321 gtaacagcct tctgggagga gggatttggg gaattatttg agaaagcaaa acaaaacaat
1381 aacaatagaa aaacttctaa tggtgatgac agcctcttct tcagtaattt ctcacttctt
1441 ggtactcctg tcctgaaaga tattaatttc aagatagaaa gaggacagtt gttggcggtt
1501 gctggatcca ctggagcagg caagacttca cttctaatga tgattatggg agaactggag
1561 ccttcagagg gtaaaattaa gcacagtgga agaatttcat tctgttctca gttttcctgg
1621 attatgcctg gcaccattaa agaaaatatc atctttggtg tttcctatga tgaatataga
1681 tacagaagcg tcatcaaagc atgccaacta gaagaggaca tctccaagtt tgcagagaaa
1741 gacaatatag ttcttggaga aggtggaatc acactgagtg gaggtcaacg agcaagaatt
1801 tctttagcaa gagcagtata caaagatgct gatttgtatt tattagactc tccttttgga
1861 tacctagatg ttttaacaga aaaagaaata tttgaaagct gtgtctgtaa actgatggct
1921 aacaaaacta ggattttggt cacttctaaa atggaacatt taaagaaagc tgacaaaata
1981 ttaattttga atgaaggtag cagctatttt tatgggacat tttcagaact ccaaaatcta
2041 cagccagact ttagctcaaa actcatggga tgtgattctt tcgaccaatt tagtgcagaa
2101 agaagaaatt caatcctaac tgagaccttа caccgtttct cattagaagg agatgctcct
2161 gtctcctgga cagaaacaaa aaaacaatct tttaaacaga ctggagagtt tggggaaaaa
2221 aggaagaatt ctattctcaa tccaatcaac tctatacgaa aattttccat tgtgcaaaag
2281 actcccttac aaatgaatgg catcgaagag gattctgatg agcctttaga gagaaggctg
2341 tccttagtac cagattctga gcagggagag gcgatactgc ctcgcatcag cgtgatcagc
2401 actggcccca cgcttcaggc acgaaggagg cagtctgtcc tgaacctgat gacacactca
2461 gttaaccaag gtcagaacat tcaccgaaag acaacagcat ccacacgaaa agtgtcactg
2521 gcccctcagg caaacttgac tgaactggat atatattcaa gaaggttatc tcaagaaact
2581 ggcttggaaa taagtgaaga aattaacgaa gaagacttaa aggagtgcct ttttgatgat
2641 atggagagca taccagcagt gactacatgg aacacatacc ttcgatatat tactgtccac
2701 aagagcttaa tttttgtgct aatttggtgc ttagtaattt ttctggcaga ggtggctgct
2761 tctttggttg tgctgtggct ccttggaaac actcctcttc aagacaaagg gaatagtact
2821 catagtagaa ataacagcta tgcagtgatt atcaccagca ccagttcgta ttatgtgttt
2881 tacatttacg tgggagtagc cgacactttg cttgctatgg gattcttcag aggtctacca
2941 ctggtgcata ctctaatcac agtgtcgaaa attttacacc acaaaatgtt acattctgtt
3001 cttcaagcac ctatgtcaac cctcaacacg ttgaaagcag gtgggattct taatagattc
3061 tccaaagata tagcaatttt ggatgacctt ctgcctctta ccatatttga cttcatccag
```

FIGURE 28A

3121 ttgttattaa ttgtgattgg agctatagca gttgtcgcag ttttacaacc ctacatcttt
3181 gttgcaacag tgccagtgat agtggctttt attatgttga gagcatattt cctccaaacc
3241 tcacagcaac tcaaacaact ggaatctgaa ggcaggagtc caattttcac tcatcttgtt
3301 acaagcttaa aaggactatg gacacttcgt gccttcggac ggcagcctta ctttgaaact
3361 ctgttccaca aagctctgaa tttacatact gccaactggt tcttgtacct gtcaacactg
3421 cgctggttcc aaatgagaat agaaatgatt tttgtcatct tcttcattgc tgttaccttc
3481 atttccattt taacaacagg agaaggagaa ggaagagttg gtattatcct gactttagcc
3541 atgaatatca tgagtacatt gcagtgggct gtaaactcca gcatagatgt ggatagcttg
3601 atgcgatctg tgagccgagt ctttaagttc attgacatgc caacagaagg taaacctacc
3661 aagtcaacca aaccatacaa gaatggccaa ctctcgaaag ttatgattat tgagaattca
3721 cacgtgaaga aagatgacat ctggccctca gggggccaaa tgactgtcaa agatctcaca
3781 gcaaaataca cagaaggtgg aaatgccata ttagagaaca tttccttctc aataagtcct
3841 ggccagaggg tgggcctctt gggaagaact ggatcaggga agagtacttt gttatcagct
3901 tttttgagac tactgaacac tgaaggagaa atccagatcg atggtgtgtc ttgggattca
3961 ataactttgc aacagtggag gaaagccttt ggagtgatac cacagaaagt atttattttt
4021 tctggaacat ttagaaaaaa cttggatccc tatgaacagt ggagtgatca agaaatatgg
4081 aaagttgcag atgaggttgg gctcagatct gtgatagaac agtttcctgg gaagcttgac
4141 tttgtccttg tggatggggg ctgtgtccta agccatggcc acaagcagtt gatgtgcttg
4201 gctagatctg ttctcagtaa ggcgaagatc ttgctgcttg atgaacccag tgctcatttg
4261 gatccagtaa cataccaaat aattagaaga actctaaaac aagcatttgc tgattgcaca
4321 gtaattctct gtgaacacag gatagaagca atgctggaat gccaacaatt tttggtcata
4381 gaagagaaca aagtgcggca gtacgattcc atccagaaac tgctgaacga gaggagcctc
4441 ttccggcaag ccatcagccc ctccgacagg gtgaagctct ttccccaccg gaactcaagc
4501 aagtgcaagt ctaagcccca gattgctgct ctgaaagagg agacagaaga agaggtgcaa
4561 gatacaaggc tttagagagc agcataaatg ttgacatggg acatttgctc atggaattgg
4621 agctcgtggg acagtcacct catggaattg gagctcgtgg aacagttacc tctgcctcag
4681 aaaacaagga tgaattaagt tttttttaa aaaagaaaca tttggtaagg ggaattgagg
4741 acactgatat gggtcttgat aaatggcttc ctggcaatag tcaaattgtg tgaaaggtac
4801 ttcaaatcct tgaagattta ccacttgtgt tttgcaagcc agattttcct gaaaaccctt
4861 gccatgtgct agtaattgga aaggcagctc taaatgtcaa tcagcctagt tgatcagctt
4921 attgtctagt gaaactcgtt aatttgtagt gttggagaag aactgaaatc atacttctta
4981 gggttatgat taagtaatga taactggaaa cttcagcggt ttatataagc ttgtattcct
5041 ttttctctcc tctccccatg atgtttagaa acacaactat attgtttgct aagcattcca
5101 actatctcat ttccaagcaa gtattagaat accacaggaa ccacaagact gcacatcaaa
5161 atatgcccca ttcaacatct agtgagcagt caggaaagag aacttccaga tcctggaaat
5221 cagggttagt attgtccagg tctaccaaaa atctcaatat ttcagataat cacaatacat
5281 cccttacctg ggaaagggct gttataatct ttcacagggg acaggatggt tcccttgatg
5341 aagaagttga tatgcctttt cccaactcca gaaagtgaca agctcacaga cctttgaact
5401 agagtttagc tggaaaagta tgttagtgca aattgtcaca ggacagccct tctttccaca
5461 gaagctccag gtagagggtg tgtaagtaga taggccatgg gcactgtggg tagacacaca
5521 tgaagtccaa gcatttagat gtataggttg atggtggtat gttttcaggc tagatgtatg
5581 tacttcatgc tgtctacact aagagagaat gagagacaca ctgaagaagc accaatcatg
5641 aattagtttt atatgcttct gttttataat tttgtgaagc aaaatttttt ctctaggaaa
5701 tatttatttt aataatgttt caaacatata ttacaatgct gtattttaaa agaatgatta
5761 tgaattacat ttgtataaaa taatttttat atttgaaata ttgacttttt atggcactag
5821 tatttttatg aaatattatg ttaaaactgg gacaggggag aacctagggt gatattaacc
5881 aggggccatg aatcaccttt tggtctggag ggaagccttg gggctgatcg agttgttgcc
5941 cacagctgta tgattcccag ccagacacag cctcttagat gcagttctga agaagatggt
6001 accaccagtc tgactgtttc catcaagggt acactgcctt ctcaactcca aactgactct
6061 taagaagact gcattatatt tattactgta agaaaatatc acttgtcaat aaaatccata
6121 catttgtgt (SEQ ID NO:49)

FIGURE 28B

CFTR (chloride channel, NM_000492)

MQRSPLEKASVVSKLFFSWTRPILRKGYRQRLELSDIYQIPSVD
SADNLSEKLEREWDRELASKKNPKLINALRRCFFWRFMFYGIFLYLGEVTKAVQPLLL
GRIIASYDPDNKEERSIAIYLGIGLCLLFIVRTLLLHPAIFGLHHIGMQMRIAMFSLI
YKKTLKLSSRVLDKISIGQLVSLLSNNLNKFDEGLALAHFVWIAPLQVALLMGLIWEL
LQASAFCGLGFLIVLALFQAGLGRMMMKYRDQRAGKISERLVITSEMIENIQSVKAYC
WEEAMEKMIENLRQTELKLTRKAAYVRYFNSSAFFFSGFFVVFLSVLPYALIKGIILR
KIFTTISFCIVLRMAVTRQFPWAVQTWYDSLGAINKIQDFLQKQEYKTLEYNLTTTEV
MENVTAFWEEGFGELFEKAKQNNNNRKTSNGDDSLFFSNFSLLGTPVLKDINFKIER
QLLAVAGSTGAGKTSLLMMIMGELEPSEGKIKHSGRISFCSQFSWIMPGTIKENIIF
VSYDEYRYRSVIKACQLEEDISKFAEKDNIVLGEGGITLSGGQRARISLARAVYKDA
LYLLDSPFGYLDVLTEKEIFESCVCKLMANKTRILVTSKMEHLKKADKILILNEGSS
FYGTFSELQNLQPDFSSKLMGCDSFDQFSAERRNSILTETLHRFSLEGDAPVSWTET
KQSFKQTGEFGEKRKNSILNPINSIRKFSIVQKTPLQMNGIEEDSDEPLERRLSLVP
SEQGEAILPRISVISTGPTLQARRRQSVLNLMTHSVNQGQNIHRKTTASTRKVSLAP
ANLTELDIYSRRLSQETGLEISEEINEEDLKECLFDDMESIPAVTTWNTYLRYITVH
SLIFVLIWCLVIFLAEVAASLVVLWLLGNTPLQDKGNSTHSRNNSYAVIITSTSSYY
FYIYVGVADTLLAMGFFRGLPLVHTLITVSKILHHKMLHSVLQAPMSTLNTLKAGGI
NRFSKDIAILDDLLPLTIFDFIQLLLIVIGAIAVVAVLQPYIFVATVPVIVAFIMLR
YFLQTSQQLKQLESEGRSPIFTHLVTSLKGLWTLRAFGRQPYFETLFHKALNLHTAN
FLYLSTLRWFQMRIEMIFVIFFIAVTFISILTTGEGEGRVGIILTLAMNIMSTLQWA
NSSIDVDSLMRSVSRVFKFIDMPTEGKPTKSTKPYKNGQLSKVMIIENSHVKKDDIW
SGGQMTVKDLTAKYTEGGNAILENISFSISPGQRVGLLGRTGSGKSTLLSAFLRLLN
EGEIQIDGVSWDSITLQQWRKAFGVIPQKVFIFSGTFRKNLDPYEQWSDQEIWKVAD
VGLRSVIEQFPGKLDFVLVDGGCVLSHGHKQLMCLARSVLSKAKILLLDEPSAHLDP
TYQIIRRTLKQAFADCTVILCEHRIEAMLECQQFLVIEENKVRQYDSIQKLLNERSL
RQAISPSDRVKLFPHRNSSKCKSKPQIAALKEETEEEVQDTRL (SEQ ID NO:50)

FIGURE 28C

H2R (histamine H2 receptor, NM_022304)

```
   1 ctcctgccct ccactgactc cagagaggga gatccccagt acttgactcc atcacgcaga
  61 tgggagcagg caccagctat ggagagggat acagctgcgt ctccacatga cccatcctgc
 121 atgacaccaa agccaccgcc agacagtgcc tcggattcta tgcaaaacct gggaagcgga
 181 gacctacccc agccccggga ggaagctagc tcttcagggg accgtctgag gactggagtt
 241 tgatccatga acctggcttc gaggccttgc ttttctctct tcttcattca tattcattcc
 301 caacacctta gaaggtgttg cttaatttat ttctagaaaa gcagcccaga gtcagtcatt
 361 gaagccttcc ccacccccctg gccaaaaaaa aaaaaaaaaa aaaactggac acattttgga
 421 tctgttggga gcttggagtc cagtggttgg catagttgtc acattgggag cagagaagaa
 481 gcaaccaggg gccctgatca ggggactgag ccgtagagtc ccaggatggc acccaatggc
 541 acagcctctt ccttttgcct ggactctacc gcatgcaaga tcaccatcac cgtggtcctt
 601 gcggtcctca tcctcatcac cgttgctggc aatgtggtcg tctgtctggc cgtgggcttg
 661 aaccgccggc tccgcaacct gaccaattgt ttcatcgtgt ccttggctat cactgacctg
 721 ctcctcggcc tcctggtgct gcccttctct gccatctacc agctgtcctg caagtggagc
 781 tttggcaagg tcttctgcaa tatctacacc agcctggatg tgatgctctg cacagcctcc
 841 attcttaacc tcttcatgat cagcctcgac cggtactgcg ctgtcatgga cccactgcgg
 901 taccctgtgc tggtcacccc agttcgggtc gccatctctc tggtcttaat ttgggtcatc
 961 tccattaccc tgtcctttct gtctatccac ctggggtgga acagcaggaa cgagaccagc
1021 aagggcaatc ataccacctc taagtgcaaa gtccaggtca atgaagtgta cgggctggtg
1081 gatgggctgg tcaccttcta cctcccgcta ctgatcatgt gcatcaccta ctaccgcatc
1141 ttcaaggtcg cccgggatca ggccaagagg atcaatcaca ttagctcctg gaaggcagcc
1201 accatcaggg agcacaaagc cacagtgaca ctggccgccg tcatgggggc cttcatcatc
1261 tgctggtttc cctacttcac cgcgtttgtg taccgtgggc tgagagggga tgatgccatc
1321 aatgaggtgt tagaagccat cgttctgtgg ctgggctatg ccaactcagc cctgaacccc
1381 atcctgtatg ctgcgctgaa cagagacttc cgcaccgggt accaacagct cttctgctgc
1441 aggctggcca accgcaactc ccacaaaact tctctgaggt ccaacgcctc tcagctgtcc
1501 aggacccaaa gccgagaacc caggcaacag gaagagaaac ccctgaagct ccaggtgtgg
1561 agtgggacag aagtcacggc cccccaggga gccacagaca ggtaatagcc ctagccattg
1621 gtgcacagga tgggggcaat gggaggggat gctactgatg ggaatgatta agggagctgc
1681 tgtttaggtg gtgctggttt atgttctagg aactcttcat gagcactttg taaacaccct
1741 cttgcttaat cctcccaacg gcccccaaag gtagaactta gctccctttt aaaaggagca
1801 cattaaaatt ctcagaggac ttggcaaggg ccgcacagct ggggcat (SEQ ID NO:51)
```

FIGURE 29A

H2R (histamine H2 receptor, NM_022304)

```
APNGTASSFCLDSTACKITITVVLAVLILITVAGNVVVCLAVG
NRRLRNLTNCFIVSLAITDLLLGLLVLPFSAIYQLSCKWSFGKVFCNIYTSLDVMLC
ASILNLFMISLDRYCAVMDPLRYPVLVTPVRVAISLVLIWVISITLSFLSIHLGWNS
NETSKGNHTTSKCKVQVNEVYGLVDGLVTFYLPLLIMCITYYRIFKVARDQAKRINH
SSWKAATIREHKATVTLAAVMGAFIICWFPYFTAFVYRGLRGDDAINEVLEAIVLWL
YANSALNPILYAALNRDFRTGYQQLFCCRLANRNSHKTSLRSNASQLSRTQSREPRQ
EEKPLKLQVWSGTEVTAPQGATDR (SEQ ID NO:52)
```

FIGURE 29B

EGFR (NM_005228)

```
   1 gagctagccc cggcggccgc cgccgcccag accggacgac aggccacctc gtcggcgtcc
  61 gcccgagtcc ccgcctcgcc gccaacgcca caaccaccgc gcacggcccc ctgactccgt
 121 ccagtattga tcgggagagc cggagcgagc tcttcgggga gcagcgatgc gaccctccgg
 181 gacggccggg gcagcgctcc tggcgctgct ggctgcgctc tgcccggcga gtcgggctct
 241 ggaggaaaag aaagtttgcc aaggcacgag taacaagctc acgcagttgg gcacttttga
 301 agatcatttt ctcagcctcc agaggatgtt caataactgt gaggtggtcc ttgggaattt
 361 ggaaattacc tatgtgcaga ggaattatga tctttccttc ttaaagacca tccaggaggt
 421 ggctggttat gtcctcattg ccctcaacac agtggagcga attcctttgg aaaacctgca
 481 gatcatcaga ggaaatatgt actacgaaaa ttcctatgcc ttagcagtct tatctaacta
 541 tgatgcaaat aaaaccggac tgaaggagct gcccatgaga aatttacagg aaatcctgca
 601 tggcgccgtg cggttcagca acaaccctgc cctgtgcaac gtggagagca tccagtggcg
 661 ggacatagtc agcagtgact ttctcagcaa catgtcgatg gacttccaga accacctggg
 721 cagctgccaa aagtgtgatc caagctgtcc caatgggagc tgctggggtg caggagagga
 781 gaactgccag aaactgacca aaatcatctg tgcccagcag tgctccgggc gctgccgtgg
 841 caagtccccc agtgactgct gccacaacca gtgtgctgca ggctgcacag gccccggga
 901 gagcgactgc ctggtctgcc gcaaattccg agacgaagcc acgtgcaagg acacctgccc
 961 cccactcatg ctctacaacc ccaccacgta ccagatggat gtgaaccccg agggcaaata
1021 cagctttggt gccacctgcg tgaagaagtg tccccgtaat tatgtggtga cagatcacgg
1081 ctcgtgcgtc cgagcctgtg gggccgacag ctatgagatg gaggaagacg gcgtccgcaa
1141 gtgtaagaag tgcgaagggc cttgccgcaa agtgtgtaac ggaataggta ttggtgaatt
1201 taaagactca ctctccataa atgctacgaa tattaaacac ttcaaaaact gcacctccat
1261 cagtggcgat ctccacatcc tgccggtggc atttaggggt gactccttca cacatactcc
1321 tcctctggat ccacaggaac tggatattct gaaaaccgta aaggaaatca cagggttttt
1381 gctgattcag gcttggcctg aaaacaggac ggacctccat gcctttgaga acctagaaat
1441 catacgcggc aggaccaagc aacatggtca gttttctctt gcagtcgtca gcctgaacat
1501 aacatccttg ggattacgct ccctcaagga gataagtgat ggagatgtga taatttcagg
1561 aaacaaaaat ttgtgctatg caaatacaat aaactggaaa aaactgtttg ggacctccgg
1621 tcagaaaacc aaaattataa gcaacagagg tgaaaacagc tgcaaggcca caggccaggt
1681 ctgccatgcc ttgtgctccc ccgagggctg ctggggcccg gagcccaggg actgcgtctc
1741 ttgccggaat gtcagccgag gcagggaatg cgtggacaag tgcaaccttc tggagggtga
1801 gccaagggag tttgtggaga actctgagtg catacagtgc cacccagagt gcctgcctca
1861 ggccatgaac atcacctgca caggacgggg accagacaac tgtatccagt gtgcccacta
1921 cattgacggc ccccactgcg tcaagacctg cccggcagga gtcatgggag aaaacaacac
1981 cctggtctgg aagtacgcag acgccggcca tgtgtgccac ctgtgccatc caaactgcac
2041 ctacggatgc actgggccag gtcttgaagg ctgtccaacg aatgggccta agatcccgtc
2101 catcgccact gggatggtgg gggccctcct cttgctgctg gtggtggccc tggggatcgg
2161 cctcttcatg cgaaggcgcc acatcgttcg gaagcgcacg ctgcggaggc tgctgcagga
2221 gagggagctt gtggagcctc ttacacccag tggagaagct cccaaccaag ctctcttgag
2281 gatcttgaag gaaactgaat tcaaaaagat caaagtgctg ggctccggtg cgttcggcac
2341 ggtgtataag ggactctgga tcccagaagg tgagaaagtt aaaattcccg tcgctatcaa
2401 ggaattaaga gaagcaacat ctccgaaagc caacaaggaa atcctcgatg aagcctacgt
2461 gatggccagc gtggacaacc cccacgtgtg ccgcctgctg ggcatctgcc tcacctccac
2521 cgtgcagctc atcacgcagc tcatgccctt cggctgcctc ctggactatg tccgggaaca
2581 caaagacaat attggctccc agtacctgct caactggtgt gtgcagatcg caaagggcat
2641 gaactacttg gaggaccgtc gcttggtgca ccgcgacctg gcagccagga acgtactggt
2701 gaaaacaccg cagcatgtca agatcacaga ttttgggctg gccaaactgc tgggtgcgga
2761 agagaaagaa taccatgcag aaggaggcaa agtgcctatc aagtggatgg cattggaatc
2821 aattttacac agaatctata cccaccagag tgatgtctgg agctacgggg tgaccgtttg
2881 ggagttgatg acctttggat ccaagccata tgacggaatc cctgccagcg agatctcctc
2941 catcctggag aaaggagaac gcctccctca gccacccata tgtaccatcg atgtctacat
3001 gatcatggtc aagtgctgga tgatagacgc agatagtcgc ccaaagttcc gtgagttgat
3061 catcgaattc tccaaaatgg cccgagaccc ccagcgctac cttgtcattc agggggatga
```

FIGURE 30A

3121 aagaatgcat ttgccaagtc ctacagactc caacttctac cgtgccctga tggatgaaga
3181 agacatggac gacgtggtgg atgccgacga gtacctcatc ccacagcagg gcttcttcag
3241 cagcccctcc acgtcacgga ctcccctcct gagctctctg agtgcaacca gcaacaattc
3301 caccgtggct tgcattgata gaaatgggct gcaaagctgt cccatcaagg aagacagctt
3361 cttgcagcga tacagctcag accccacagg cgccttgact gaggacagca tagacgacac
3421 cttcctccca gtgcctgaat acataaacca gtccgttccc aaaaggcccg ctggctctgt
3481 gcagaatcct gtctatcaca atcagcctct gaaccccgcg cccagcagag acccacacta
3541 ccaggacccc cacagcactg cagtgggcaa ccccgagtat ctcaacactg tccagcccac
3601 ctgtgtcaac agcacattcg acagccctgc ccactgggcc cagaaaggca gccaccaaat
3661 tagcctggac aaccctgact accagcagga cttctttccc aaggaagcca agccaaatgg
3721 catctttaag ggctccacag ctgaaaatgc agaataccta agggtcgcgc cacaaagcag
3781 tgaatttatt ggagcatgac cacggaggat agtatgagcc ctaaaaatcc agactctttc
3841 gatacccagg accaagccac agcaggtcct ccatcccaac agccatgccc gcattagctc
3901 ttagacccac agactggttt tgcaacgttt acaccgacta gccaggaagt acttccacct
3961 cgggcacatt ttgggaagtt gcattccttt gtcttcaaac tgtgaagcat ttacagaaac
4021 gcatccagca agaatattgt ccctttgagc agaaatttat ctttcaaaga ggtatatttg
4081 aaaaaaaaaa aaaaagtata tgtgaggatt tttattgatt ggggatcttg gagtttttca
4141 ttgtcgctat tgatttttac ttcaatgggc tcttccaaca aggaagaagc ttgctggtag
4201 cacttgctac cctgagttca tccaggccca actgtgagca aggagcacaa gccacaagtc
4261 ttccagagga tgcttgattc cagtggttct gcttcaaggc ttccactgca aaacactaaa
4321 gatccaagaa ggccttcatg gccccagcag gccggatcgg tactgtatca agtcatggca
4381 ggtacagtag gataagccac tctgtccctt cctgggcaaa gaagaaacgg aggggatgaa
4441 ttcttcctta gacttacttt tgtaaaaatg tccccacggt acttactccc cactgatgga
4501 ccagtggttt ccagtcatga gcgttagact gacttgtttg tcttccattc cattgttttg
4561 aaactcagta tgccgcccct gtcttgctgt catgaaatca gcaagagagg atgacacatc
4621 aaataataac tcggattcca gcccacattg gattcatcag catttggacc aatagcccac
4681 agctgagaat gtggaatacc taaggataac accgcttttg ttctcgcaaa aacgtatctc
4741 ctaatttgag gctcagatga aatgcatcag gtcctttggg gcatagatca gaagactaca
4801 aaaatgaagc tgctctgaaa tctcctttag ccatcacccc aacccccaa aattagtttg
4861 tgttacttat ggaagatagt tttctccttt tacttcactt caaaagcttt ttactcaaag
4921 agtatatgtt ccctccaggt cagctgcccc caaacccccc ccttacgctt tgtcacacaa
4981 aaagtgtctc tgccttgagt catctattca agcacttaca gctctggcca caacagggca
5041 ttttacaggt gcgaatgaca gtagcattat gagtagtgtg aattcaggta gtaaatatga
5101 aactagggtt tgaaattgat aatgctttca caacatttgc agatgtttta gaaggaaaaa
5161 agttccttcc taaaataatt tctctacaat tggaagattg gaagattcag ctagttagga
5221 gcccatttttt tcctaatctg tgtgtgccct gtaacctgac tggttaacag cagtcctttg
5281 taaacagtgt tttaaactct cctagtcaat atccacccca tccaatttat caaggaagaa
5341 atggttcaga aaatattttc agcctacagt tatgttcagt cacacacaca tacaaaatgt
5401 tccttttgct tttaaagtaa tttttgactc ccagatcagt cagagcccct acagcattgt
5461 taagaaagta tttgattttt gtctcaatga aaataaaact atattcattt cc (SEQ ID
NO:53)

FIGURE 30B

EGFR (NM_005228)

RPSGTAGAALLALLAALCPASRALEEKKVCQGTSNKLTQLGTF
DHFLSLQRMFNNCEVVLGNLEITYVQRNYDLSFLKTIQEVAGYVLIALNTVERIPLE
LQIIRGNMYYENSYALAVLSNYDANKTGLKELPMRNLQEILHGAVRFSNNPALCNVE
IQWRDIVSSDFLSNMSMDFQNHLGSCQKCDPSCPNGSCWGAGEENCQKLTKIICAQQ
SGRCRGKSPSDCCHNQCAAGCTGPRESDCLVCRKFRDEATCKDTCPPLMLYNPTTYQ
DVNPEGKYSFGATCVKKCPRNYVVTDHGSCVRACGADSYEMEEDGVRKCKKCEGPCR
VCNGIGIGEFKDSLSINATNIKHFKNCTSISGDLHILPVAFRGDSFTHTPPLDPQEL
ILKTVKEITGFLLIQAWPENRTDLHAFENLEIIRGRTKQHGQFSLAVVSLNITSLGL
SLKEISDGDVIISGNKNLCYANTINWKKLFGTSGQKTKIISNRGENSCKATGQVCHA
CSPEGCWGPEPRDCVSCRNVSRGRECVDKCNLLEGEPREFVENSECIQCHPECLPQA
NITCTGRGPDNCIQCAHYIDGPHCVKTCPAGVMGENNTLVWKYADAGHVCHLCHPNC
YGCTGPGLEGCPTNGPKIPSIATGMVGALLLLLVVALGIGLFMRRRHIVRKRTLRRL
QERELVEPLTPSGEAPNQALLRILKETEFKKIKVLGSGAFGTVYKGLWIPEGEKVKI
VAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTVQLITQLMPFGCL
DYVREHKDNIGSQYLLNWCVQIAKGMNYLEDRRLVHRDLAARNVLVKTPQHVKITDF
LAKLLGAEEKEYHAEGGKVPIKWMALESILHRIYTHQSDVWSYGVTVWELMTFGSKP
DGIPASEISSILEKGERLPQPPICTIDVYMIMVKCWMIDADSRPKFRELIIEFSKMA
DPQRYLVIQGDERMHLPSPTDSNFYRALMDEEDMDDVVDADEYLIPQQGFFSSPSTS
TPLLSSLSATSNNSTVACIDRNGLQSCPIKEDSFLQRYSSDPTGALTEDSIDDTFLP
PEYINQSVPKRPAGSVQNPVYHNQPLNPAPSRDPHYQDPHSTAVGNPEYLNTVQPTC
NSTFDSPAHWAQKGSHQISLDNPDYQQDFFPKEAKPNGIFKGSTAENAEYLRVAPQS
EFIGA (SEQ ID NO:54)

FIGURE 30C

EPHB2 (NM_004442)

```
   1 gccccgggaa gcgcagccat ggctctgcgg aggctggggg ccgcgctgct gctgctgccg
  61 ctgctcgccg ccgtggaaga aacgctaatg gactccacta cagcgactgc tgagctgggc
 121 tggatggtgc atcctccatc agggtgggaa gaggtgagtg gctacgatga gaacatgaac
 181 acgatccgca cgtaccaggt gtgcaacgtg tttgagtcaa gccagaacaa ctggctacgg
 241 accaagttta tccggcgccg tggcgcccac cgcatccacg tggagatgaa gttttcggtg
 301 cgtgactgca gcagcatccc cagcgtgcct ggctcctgca aggagacctt caacctctat
 361 tactatgagg ctgactttga ctcggccacc aagaccttcc ccaactggat ggagaatcca
 421 tgggtgaagg tggataccat tgcagccgac gagagcttct cccaggtgga cctgggtggc
 481 cgcgtcatga aaatcaacac cgaggtgcgg agcttcggac ctgtgtcccg cagcggcttc
 541 tacctggcct tccaggacta tggcggctgc atgtccctca tcgccgtgcg tgtcttctac
 601 cgcaagtgcc cccgcatcat ccagaatggc gccatcttcc aggaaaccct gtcgggggct
 661 gagagcacat cgctggtggc tgcccggggc agctgcatcg ccaatgcgga agaggtggat
 721 gtacccatca agctctactg taacggggac ggcgagtggc tggtgcccat cgggcgctgc
 781 atgtgcaaag caggcttcga ggccgttgag aatggcaccg tctgccgagg ttgtccatct
 841 gggactttca aggccaacca aggggatgag gcctgtaccc actgtcccat caacagccgg
 901 accacttctg aaggggccac caactgtgtc tgccgcaatg gctactacag agcagacctg
 961 gacccccctgg acatgccctg cacaaccatc ccctccgcgc cccaggctgt gatttccagt
1021 gtcaatgaga cctccctcat gctggagtgg acccctcccc gcgactccgg aggccgagag
1081 gacctcgtct acaacatcat ctgcaagagc tgtggctcgg gccggggtgc ctgcacccgc
1141 tgcggggaca atgtacagta cgcaccacgc cagctaggcc tgaccgagcc acgcatttac
1201 atcagtgacc tgctggccca cacccagtac accttcgaga tccaggctgt gaacggcgtt
1261 actgaccaga gccccttctc gcctcagttc gcctctgtga acatcaccac caaccaggca
1321 gctccatcgg cagtgtccat catgcatcag gtgagccgca ccgtggacag cattaccctg
1381 tcgtggtccc agccggacca gcccaatggc gtgatcctgg actatgagct gcagtactat
1441 gagaaggagc tcagtgagta caacgccaca gccataaaaa gccccaccaa cacggtcacc
1501 gtgcagggcc tcaaagccgg cgccatctat gtcttccagg tgcgggcacg caccgtggca
1561 ggctacgggc gctacagcgg caagatgtac ttccagacca tgacagaagc cgagtaccag
1621 acaagcatcc aggagaagtt gccactcatc atcggctcct cggccgctgg cctggtcttc
1681 ctcattgctg tggttgtcat cgccatcgtg tgtaacagaa gacgggggtt tgagcgtgct
1741 gactcggagt acacggacaa gctgcaacac tacaccagtg gccacatgac cccaggcatg
1801 aagatctaca tcgatccttt cacctacgag gaccccaacg aggcagtgcg ggagtttgcc
1861 aaggaaattg acatctcctg tgtcaaaatt gagcaggtga tcggagcagg ggagtttggc
1921 gaggtctgca gtggccacct gaagctgcca ggcaagagag agatctttgt ggccatcaag
1981 acgctcaagt cgggctacac ggagaagcag cgccgggact tcctgagcga agcctccatc
2041 atgggccagt tcgaccatcc caacgtcatc cacctggagg gtgtcgtgac caagagcaca
2101 cctgtgatga tcatcaccga gttcatggag aatggctccc tggactcctt tctccggcaa
2161 aacgatgggc agttcacagt catccagctg gtgggcatgc ttcggggcat cgcagctggc
2221 atgaagtacc tggcagacat gaactatgtt caccgtgacc tggctgcccg caacatcctc
2281 gtcaacagca acctggtctg caaggtgtcg gactttgggc tctcacgctt tctagaggac
2341 gatacctcag accccaccta caccagtgcc ctgggcggaa agatccccat ccgctggaca
2401 gccccggaag ccatccagta ccggaagttc acctcggcca gtgatgtgtg gagctacggc
2461 attgtcatgt gggaggtgat gtcctatggg gagcggccct actgggacat gaccaaccag
2521 gatgtaatca atgccattga gcaggactat cggctgccac cgcccatgga ctgcccgagc
2581 gccctgcacc aactcatgct ggactgttgg cagaaggacc gcaaccaccg gcccaagttc
2641 ggccaaattg tcaacacgct agacaagatg atccgcaatc ccaacagcct caaagccatg
2701 gcgcccctct cctctggcat caacctgccg ctgctggacc gcacgatccc cgactacacc
2761 agctttaaca cggtggacga gtggctggag gccatcaaga tggggcagta caaggagagc
2821 ttcgccaatg ccggcttcac ctcctttgac gtcgtgtctc agatgatgat ggaggacatt
2881 ctccgggttg gggtcacttt ggctggccac cagaaaaaaa tcctgaacag tatccaggtg
2941 atgcgggcgc agatgaacca gattcagtct gtggaggttt gacattcacc tgcctcggct
3001 cacctcttcc tccaagcccc gccccctctg ccccacgtgc cggccctcct ggtgctctat
```

FIGURE 31A

3061 ccactgcagg gccagccact cgccaggagg ccacgggcca cgggaagaac caagcggtgc
3121 cagccacgag acgtcaccaa gaaaacatgc aactcaaacg acggaaaaaa aaagggaatg
3181 ggaaaaaaga aaacagatcc tgggaggggg cgggaaatac aaggaatatt ttttaaagag
3241 gattctcata aggaaagcaa tgactgttct tgcgggggat aaaaaagggc ttgggagatt
3301 catgcgatgt gtccaatcgg agacaaaagc agtttctctc caactccctc tgggaaggtg
3361 acctggccag agccaagaaa cactttcaga aaaacaaatg tgaaggggag agacaggggc
3421 cgcccttggc tcctgtccct gctgctcctc taggcctcac tcaacaacca agcgcctgga
3481 ggacgggaca gatggacaga cagccaccct gagaacccct ctgggaaaat ctattcctgc
3541 caccactggg caaacagaag aatttttctg tctttggaga gtattttaga aactccaatg
3601 aaagacactg tttctcctgt tggctcacag ggctgaaagg ggcttttgtc ctcctgggtc
3661 agggagaacg cggggacccc agaaaggtca gccttcctga ggatgggcaa cccccaggtc
3721 tgcagctcca ggtacatatc acgcgcacag cctggcagcc tggccctcct ggtgcccact
3781 cccgccagcc cctgcctcga ggactgatac tgcagtgact gccgtcagct ccgactgccg
3841 ctgagaaggg ttgatcctgc atctgggttt gtttacagca attcctggac tcgggggtat
3901 tttggtcaca gggtggtttt ggtttagggg gtttgtttgt tgggttgttt tttgtttttt
3961 ggtttttttt aatgacaatg aagtgacact ttgacatttc ctacctttg aggacttgat
4021 ccttctccag gaagaaggtg ctttctgctt actgacttag gcaatacacc aagggcgaga
4081 ttttatatgc acatttctgg atttttttat acggttttca ttgacactct tccctcctcc
4141 cacctgccac caggcctcac caaagcccac tgccatgggg ccatctgggc cattcagaga
4201 ctggagtgag atttgggtgt ggaggggggag gcgccaaggt ggaggagctt cccactccag
4261 gactgttgat gaaagggaca gattgaggag gaagtgggct ctgaggctgc agggctggaa
4321 gtccttgccc acttcccact ctcctgcccc aatctatcta gtacttccca ggcaaatagg
4381 ccccttgag gctcctgagt gccctcagat ggtcaaaacc cagttttccc tctgggagcc
4441 taaaccaggc tgcatcggag gccaggaccc ggatcattca ctgtgatacc ctgccctcca
4501 gagggtgcgc tcagagacac gggcaagcat gcctcttccc ttccctggag agaaagtgtg
4561 tgatttctct cccacctcct tccccccacc agaccttgc tgggcctaaa ggtcttggcc
4621 atggggacgc cctcagtcta gggatctggc cacagactcc ctcctgtgaa ccaacacaga
4681 cacccaagca gagcaatcag ttagtgaatt g (SEQ ID NO:55)

FIGURE 31B

EPHB2 (NM_004442)

ALRRLGAALLLLPLLAAVEETLMDSTTATAELGWMVHPPSGWE
VSGYDENMNTIRTYQVCNVFESSQNNWLRTKFIRRRGAHRIHVEMKFSVRDCSSIPS
PGSCKETFNLYYYEADFDSATKTFPNWMENPWVKVDTIAADESFSQVDLGGRVMKIN
EVRSFGPVSRSGFYLAFQDYGGCMSLIAVRVFYRKCPRIIQNGAIFQETLSGAESTS
VAARGSCIANAEEVDVPIKLYCNGDGEWLVPIGRCMCKAGFEAVENGTVCRGCPSGT
KANQGDEACTHCPINSRTTSEGATNCVCRNGYYRADLDPLDMPCTTIPSAPQAVISS
NETSLMLEWTPPRDSGGREDLVYNIICKSCGSGRGACTRCGDNVQYAPRQLGLTEPR
YISDLLAHTQYTFEIQAVNGVTDQSPFSPQFASVNITTNQAAPSAVSIMHQVSRTVD
ITLSWSQPDQPNGVILDYELQYYEKELSEYNATAIKSPTNTVTVQGLKAGAIYVFQV
ARTVAGYGRYSGKMYFQTMTEAEYQTSIQEKLPLIIGSSAAGLVFLIAVVVIAIVCN
RRGFERADSEYTDKLQHYTSGHMTPGMKIYIDPFTYEDPNEAVREFAKEIDISCVKI
QVIGAGEFGEVCSGHLKLPGKREIFVAIKTLKSGYTEKQRRDFLSEASIMGQFDHPN
IHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRGIAAGMKYLAD
NYVHRDLAARNILVNSNLVCKVSDFGLSRFLEDDTSDPTYTSALGGKIPIRWTAPEA
QYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPMDCPSAL
QLMLDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTIPDYT
FNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRVGVTLAGHQKKILNSI
VMRAQMNQIQSVEV (SEQ ID NO:56)

FIGURE 31C

CRIPTO CR-1 (NM_003212)

```
   1 ggagaatccc cggaaaggct gagtctccag ctcaaggtca aaacgtccaa ggccgaaagc
  61 cctccagttt cccctggacg ccttgctcct gcttctgcta cgaccttctg gggaaaacga
 121 atttctcatt ttcttcttaa attgccattt tcgctttagg agatgaatgt tttcctttgg
 181 ctgttttggc aatgactctg aattaaagcg atgctaacgc ctcttttccc cctaattgtt
 241 aaaagctatg gactgcagga agatggcccg cttctcttac agtgtgattt ggatcatggc
 301 catttctaaa gtctttgaac tgggattagt tgccgggctg ggccatcagg aatttgctcg
 361 tccatctcgg ggatacctgg ccttcagaga tgacagcatt tggccccagg aggagcctgc
 421 aattcggcct cggtcttccc agcgtgtgcc gcccatgggg atacagcaca gtaaggagct
 481 aaacagaacc tgctgcctga atgggggaac ctgcatgctg gggtcctttt gtgcctgccc
 541 tccctccttc tacggacgga actgtgagca cgatgtgcgc aaagagaact gtgggtctgt
 601 gccccatgac acctggctgc ccaagaagtg ttccctgtgt aaatgctggc acggtcagct
 661 ccgctgcttt cctcaggcat ttctacccgg ctgtgatggc cttgtgatgg atgagcacct
 721 cgtggcttcc aggactccag aactaccacc gtctgcacgt actaccactt ttatgctagt
 781 tggcatctgc ctttctatac aaagctacta ttaatcgaca ttgacctatt tccagaaata
 841 caattttaga tatcatgcaa atttcatgac cagtaaaggc tgctgctaca atgtcctaac
 901 tgaaagatga tcatttgtag ttgccttaaa ataatgaata caatttccaa aatggtctct
 961 aacatttcct tacagaacta cttcttactt ctttgccctg ccctctccca aaaaactact
1021 tctttttca aaagaaagtc agccatatct ccattgtgcc taagtccagt gtttctttt
1081 ttttttttt ttgagacgga gtctcactct gtcacccagg ctggactgca atgacgcgat
1141 cttggttcac tgcaacctcc gcatccgggg ttcaagccat tctcctgcct aagcctccca
1201 agtaactggg attacaggca tgtgtcacca tgcccagcta attttttgt attttagtag
1261 agatgggggt ttcaccatat tggccagtct ggtctcgaac tctgaccttg tgatccatcg
1321 atcagcctct cgagtgctga gattacacac gtgagcaact gtgcaaggcc tggtgtttct
1381 tgatacatgt aattctacca aggtcttctt aatatgttct tttaaatgat tgaattatat
1441 gttcagatta ttggagacta attctaatgt ggaccttaga atacagtttt gagtagagtt
1501 gatcaaaatc aattaaaata gtctctttaa aaggaaagaa aacatcttta aggggaggaa
1561 ccagagtgct gaaggaatgg aagtccatct gcgtgtgtgc agggagactg ggtaggaaag
1621 aggaagcaaa tagaagagag aggttgaaaa acaaaatggg ttacttgatt ggtgattagg
1681 tggtggtaga gaagcaagta aaaaggctaa atggaagggc aagtttccat catctataga
1741 aagctatata agacaagaac tccccttttt ttcccaaagg cattataaaa agaatgaagc
1801 ctccttagaa aaaaaattat acctcaatgt ccccaacaag attgcttaat aaattgtgtt
1861 tcctccaagc tattcaattc ttttaactgt tgtagaagac aaaatgttca caatatattt
1921 agttgtaaac caagtgatca aactacatat tgtaaagccc atttttaaaa tacattgtat
1981 atatgtgtat gcacagtaaa aatggaaact atattgacct aaaaaaaaaa aaa (SEQ ID
NO:57)
```

FIGURE 32A

CRIPTO CR-1 (NM_003212)

```
DCRKMARFSYSVIWIMAISKVFELGLVAGLGHQEFARPSRGYL
FRDDSIWPQEEPAIRPRSSQRVPPMGIQHSKELNRTCCLNGGTCMLGSFCACPPSFY
RNCEHDVRKENCGSVPHDTWLPKKCSLCKCWHGQLRCFPQAFLPGCDGLVMDEHLVA
RTPELPPSARTTTFMLVGICLSIQSYY (SEQ ID NO:58)
```

FIGURE 32B

Eprin B1 (NM_004429)

```
   1 gagtagacag cacagcggca gcggagggag tctatgcgag ctggacagca gtgggaggtt
  61 tgtgaggctc gcactggccg cagaccctcg ggctcgatcg cccgggagcc aggactcggc
 121 gacgcgaggc tgccgggcta cccggccgag gcttcggggg cgcaaactaa tgggactggc
 181 tcgctcggca gcatctcccc gctcttctaa gtacactgag cagggcccgc gctgaagtag
 241 aagctgtccg ggggcgcgta gcccggagtc ccagtgtggc ccggaggaac ggagcccgtg
 301 ccagggcggc ccagtcggga gcccggggac cgagcttgtg ctgtggggaa acccccactt
 361 cttccaaggg acagcgatcc cgggacggtc gaggcgtcgg ggcggtcacc gagacctctg
 421 cgggaagacc ccgtcgggga gagggcgcgc agccccgaag cgtctcggga agtcgagcgg
 481 aatcgggcgg gatcacccgg gggcgcagag cccccgtcgc gcctcgtgcg gcagcggaga
 541 gcccaggaga acgagccctc gggggccgaa gcccatgccc gggttggggg cggctgccca
 601 gtgagtcctc ctggccggcc gggcggagaa gagcgacacc gaagccggcg ggaggggagc
 661 acttcaaggc cggcggctgc ggaggatggg cgcctgagcg gctccgagcg cagcgcggca
 721 gaggaaggcg aggcgagctt tggtgaggag gcgccaaggg atcccgaagt gcagtctgcc
 781 cccgggaaga tggctcggcc tgggcagcgt tggctcggca agtggcttgt ggcgatggtc
 841 gtgtgggcgc tgtgccggct cgccacaccg ctggccaaga acctggagcc cgtatcctgg
 901 agctccctca accccaagtt cctgagtggg aagggcttgg tgatctatcc gaaaattgga
 961 gacaagctgg acatcatctg cccccgagca gaagcagggc ggccctatga gtactacaag
1021 ctgtacctgg tgcggcctga gcaggcagct gcctgtagca cagttctcga ccccaacgtg
1081 ttggtcacct gcaataggcc agagcaggaa atacgcttta ccatcaagtt ccaggagttc
1141 agccccaact acatgggcct ggagttcaag aagcaccatg attactacat tacctcaaca
1201 tccaatggaa gcctggaggg gctggaaaac cgggagggcg gtgtgtgccg cacacgcacc
1261 atgaagatca tcatgaaggt tgggcaagat cccaatgctg tgacgcctga gcagctgact
1321 accagcaggc ccagcaagga ggcagacaac actgtcaaga tggccacaca ggcccctggt
1381 agtcggggct ccctgggtga ctctgatggc aagcatgaga ctgtgaacca ggaagagaag
1441 agtggcccag gtgcaagtgg gggcagcagc ggggaccctg atggcttctt caactccaag
1501 gtggcattgt tcgcggctgt cggtgccggt tgcgtcatct tcctgctcat catcatcttc
1561 ctgacggtcc tactactgaa gctacgcaag cggcaccgca agcacacaca gcagcgggcg
1621 gctgccctct cgctcagtac cctggccagt cccaaggggg gcagtggcac agcgggcacc
1681 gagcccagcg acatcatcat tcccttacgg actacagaga acaactactg cccccactat
1741 gagaaggtga gtggggacta cgggcaccct gtctacatcg tccaagagat gccgccccag
1801 agcccggcga acatctacta caaggtctga gtgcccggca cggcctcagg cccccgaggg
1861 acagtcggcc tggaccggac ctctcctttc gcccccacac cccctcccct tgccagctgt
1921 gcccaccttt gtatttagtt ttgtagtttc ttggctttta taatcccccc tttcccctgc
1981 cccctgggct tcggaggggg gtgcttgtgc ccctaacccc catgctcttg tgccttcccc
2041 ctctggccag gcctctgggc tccgtggggg cgccccttct tggaaggcag ggctggacac
2101 tgatggacag caggcaggga gacagtcccc tggccctgcc cctccctcgc ccccttgcc
2161 accttcccag gactgcttgt ccgctatcat cactgttttt aatgcttttg tgttcatttt
2221 ttagctgtca actcattttc atctgttttt tgaagaaaaa tggaaaaatg taaaaggcag
2281 cccctcccca ggctttgtga gcctggccca agccagtaca agagggcctg gggcacgatg
2341 tggtcagcca ggaagcatag gatgccattt cttttataga ttccttggta tttctggtgg
2401 ggtaaggggc aggccagggc tgttcacgcc catgagggaa gaggaaagtg ccactgggca
2461 aggtgtccca ccctcccctc ctgaccctcc tacgaggctt atcctggcaa tggggtagtc
2521 actgccaccc ttccacacac acacacacac acacacacac aaaaaaaaat cccttccttg
2581 tgggattctt gggcatctcc tgcctccctc actctcacgg taattaatgt cttaattggc
2641 tgttgcctgg ggaacaggag agctgctgca ggcagatgac ctcatggggg gtggagggag
2701 gtgaggtgcc caggtggcta tttgccctgc agagctggga gtttcacccc caccccccac
2761 cctgttctct ccttaccttt ggcatccttt ggcctggtgg ggaaacagag gcccagggtg
2821 gagacctaag cgggtataag accaggtggc ctgctccttt tctgggccct agcacaggtg
2881 ggtaaccccc acccaaccca gctcctgctg ctgtcccagt cttgggctgg ggcctggaaa
2941 gaggaagagg ctgcctgggg ctgggccagc ccgctgtgca ctttgacccc agttccttgc
3001 cagcacggct gctaacagac tgccacttga gtgcgccttg caggcactcc cagagcagcc
3061 atggaaggag ctggccctca caccatccac ctccacactg cctcctggcc agctgcccac
3121 cccagtgcca ggtgggagag ggagcagaac agccagcccc ttccaggtgg cagtcggaag
3181 ggtttttgtt tttgtttctg ttgccatttg tgtaaatact agtcttttttg gaaaaaaaat
3241 aatgtaaaga tgttttgtat aaactctgaa ttattttctt gttgcttttt tcttagaaaa
3301 aaatgagaac taaaaaaaaa aaattaacca catggaaaaa aaaaaa (SEQ ID NO:59)
```

FIGURE 33A

Eprin B1 (NM_004429)

MARPGQRWLGKWLVAMVVWALCRLATPLAKNLEPVSWSSLNPKF
LSGKGLVIYPKIGDKLDIICPRAEAGRPYEYYKLYLVRPEQAAACSTVLDPNVLVTCN
RPEQEIRFTIKFQEFSPNYMGLEFKKHHDYYITSTSNGSLEGLENREGGVCRTRTMKI
IMKVGQDPNAVTPEQLTTSRPSKEADNTVKMATQAPGSRGSLGDSDGKHETVNQEEKS
GPGASGGSSGDPDGFFNSKVALFAAVGAGCVIFLLIIIFLTVLLLKLRKRHRKHTQQR
AAALSLSTLASPKGGSGTAGTEPSDIIIPLRTTENNYCPHYEKVSGDYGHPVYIVQEM
PPQSPANIYYKV (SEQ ID NO:60)

FIGURE 33B

MMP-17/MT4-MMP (NM_016155)

```
   1 ccggcggggg cgccgcggag agcggagggc gccgggctgc ggaacgcgaa gcggagggcg
  61 cgggaccctg cacgccgccc gcgggcccat gtgagcgcca tgcggcgccg cgcagcccgg
 121 ggacccggcc cgccgccccc agggcccgga ctctcgcggt tgccgctgct gccgctgccg
 181 ctgctgctgc tgctggcgct ggggacccgc gggggctgcg ccgcgcccgc acccgcgccg
 241 cgcgccgagg acctcagcct gggagtggag tggctaagca ggttcggtta cctgcccccg
 301 gctgacccca caacagggca gctgcagacg caagaggagc tgtctaaggc catcacagcc
 361 atgcagcagt ttggtggcct ggaggccacc ggcatcctgg acgaggccac cctggccctg
 421 atgaaaaccc cacgctgctc cctgccagac ctccctgtcc tgacccaggc tcgcaggaga
 481 cgccaggctc cagcccccac caagtggaac aagaggaacc tgtcgtggag ggtccggacg
 541 ttcccacggg actcaccact ggggcacgac acggtgcgtg cactcatgta ctacgccctc
 601 aaggtctgga gcgacattgc gcccctgaac ttccacgagg tggcgggcag caccgccgac
 661 atccagatcg acttctccaa ggccgaccat aacgacggct acccccttcga cggccccggc
 721 ggcaccgtgg cccacgcctt cttccccggc caccaccaca ccgccgggga cacccacttt
 781 gacgatgacg aggcctggac cttccgctcc tcggatgccc acgggatgga cctgtttgca
 841 gtggctgtcc acgagtttgg ccacgccatt gggttaagcc atgtggccgc tgcacactcc
 901 atcatgcggc cgtactacca gggcccggtg ggtgacccgc tgcgctacgg gctcccctac
 961 gaggacaagg tgcgcgtctg gcagctgtac ggtgtgcggg agtctgtgtc tcccacggcg
1021 cagcccgagg agcctcccct gctgccggag cccccagaca accggtccag cgccccgccc
1081 aggaaggacg tgccccacag atgcagcact cactttgacg cggtggccca gatccgcggt
1141 gaagctttct tcttcaaagg caagtacttc tggcggctga cgcgggaccg gcacctggtg
1201 tccctgcagc cggcacagat gcaccgcttc tggcggggcc tgccgctgca cctggacagc
1261 gtggacgccg tgtacgagcg caccagcgac cacaagatcg tcttctttaa aggagacagg
1321 tactgggtgt tcaaggacaa taacgtagag gaaggatacc cgcgccccgt ctccgacttc
1381 agcctcccgc ctggcggcat cgacgctgcc ttctcctggg cccacaatga caggacttat
1441 ttctttaagg accagctgta ctggcgctac gatgaccaca cgaggcacat ggaccccggc
1501 taccccgccc agagcccccc gtggaggggt gtccccagca cgctggacga cgccatgcgc
1561 tggtccgacg gtgcctccta cttcttccgt ggccaggagt actggaaagt gctggatggc
1621 gagctggagg tggcacccgg gtacccacag tccacggccc gggactggct ggtgtgtgga
1681 gactcacagg ccgatggatc tgtggctgcg ggcgtggacg cggcagaggg gccccgcgcc
1741 cctccaggac aacatgacca gagccgctcg gaggacggtt acgaggtctg ctcatgcacc
1801 tctggggcat cctctccccc gggggcccca ggcccactgg tggctgccac catgctgctg
1861 ctgctgccgc cactgtcacc aggcgccctg tggacagcgg cccaggccct gacgctatga
1921 cacacagcgc gagcccatga gaggacagag gcggtgggac agcctggcca cagagggcaa
1981 ggactgtgcc ggagtccctg ggggaggtgc tggcgcggga tgaggacggg ccaccctggc
2041 accggaaggc cagcagaggg cacggcccgc cagggctggg caggctcagg tggcaaggac
2101 ggagctgtcc cctagtgagg gactgtgttg actgacgagc cgaggggtgg ccgctccaga
2161 agggtgccca gtcaggccgc accgccgcca gcctcctccg gccctggagg gagcatctcg
2221 ggctgggggc ccacccctct ctgtgccggc gccaccaacc ccacccacac tgctgcctgg
2281 tgctcccgcc ggcccacagg gcctccgtcc ccaggtcccc agtggggcag ccctccccac
2341 agacgagccc cccacatggt gccgcggcac gtccccctg tgacgcgttc cagaccaaca
2401 tgacctctcc ctgctttgta aaaaaaaaaa aaaaaaaa (SEQ ID NO:61)
```

FIGURE 34A

MMP-17/MT4-MMP (NM_016155)

MRRRAARGPGPPPPGPGLSRLPLLPLPLLLLLLALGTRGGCAAPA
PAPRAEDLSLGVEWLSRFGYLPPADPTTGQLQTQEELSKAITAMQQFGGLEATGILDE
ATLALMKTPRCSLPDLPVLTQARRRRQAPAPTKWNKRNLSWRVRTFPRDSPLGHDTVR
ALMYYALKVWSDIAPLNFHEVAGSTADIQIDFSKADHNDGYPFDGPGGTVAHAFFPGH
HHTAGDTHFDDDEAWTFRSSDAHGMDLFAVAVHEFGHAIGLSHVAAAHSIMRPYYQGP
VGDPLRYGLPYEDKVRVWQLYGVRESVSPTAQPEEPPLLPEPPDNRSSAPPRKDVPHR
CSTHFDAVAQIRGEAFFFKGKYFWRLTRDRHLVSLQPAQMHRFWRGLPLHLDSVDAVY
ERTSDHKIVFFKGDRYWVFKDNNVEEGYPRPVSDFSLPPGGIDAAFSWAHNDRTYFFK
DQLYWRYDDHTRHMDPGYPAQSPLWRGVPSTLDDAMRWSDGASYFFRGQEYWKVLDGE
LEVAPGYPQSTARDWLVCGDSQADGSVAAGVDAAEGPRAPPGQHDQSRSEDGYEVCSC
TSGASSPPGAPGPLVAATMLLLLPPLSPGALWTAAQALTL (SEQ ID NO:62)

FIGURE 34B

MMP26 (NM_021801)

```
      1 gacaaatgag ggtttggcat gcagctcgtc atcttaagag ttactatctt cttgccctgg
     61 tgtttcgccg ttccagtgcc ccctgctgca gaccataaag gatgggactt tgttgagggc
    121 tatttccatc aatttttcct gaccgagaag gagtcgccac tccttaccca ggagacacaa
    181 acacagctcc tgcaacaatt ccatcggaat gggacagacc tacttgacat gcagatgcat
    241 gctctgctac accagcccca ctgtggggtg cctgatgggt ccgacacctc catctcgcca
    301 ggaagatgca agtggaataa gcacactcta acttacagga ttatcaatta cccacatgat
    361 atgaagccat ccgcagtgaa agacagtata tataatgcag tttccatctg gagcaatgtg
    421 acccctttga tattccagca agtgcagaat ggagatgcag acatcaaggt ttctttctgg
    481 cagtgggccc atgaagatgg ttggcccttt gatgggccag gtggtatctt aggccatgcc
    541 tttttaccaa attctggaaa tcctggagtt gtccattttg acaagaatga acactggtca
    601 gcttcagaca ctggatataa tctgttcctg gttgcaactc atgagattgg gcattctttg
    661 ggcctgcagc actctgggaa tcagagctcc ataatgtacc ccacttactg gtatcacgac
    721 cctagaacct tccagctcag tgccgatgat atccaaagga tccagcattt gtatggagaa
    781 aaatgttcat ctgacatacc ttaatgttag cacagaggac ttattcaacc tgtcctttca
    841 gggagtttat tggaggatca aagaactgaa agcactagag cagccttggg gactgctagg
    901 atgaagccct aaagaatgca acctagtcag gttagctgaa ccgacactca aaacgctact
    961 gagtcacaat aaagattgtt ttaaagagta aaaaaaaaaa aaaaaaaaa (SEQ ID
NO:63)
```

FIGURE 35A

MMP26 (NM_021801)

```
MQLVILRVTIFLPWCFAVPVPPAADHKGWDFVEGYFHQFFLTEK
SPLLTQETQTQLLQQFHRNGTDLLDMQMHALLHQPHCGVPDGSDTSISPGRCKWNKH
LTYRIINYPHDMKPSAVKDSIYNAVSIWSNVTPLIFQQVQNGDADIKVSFWQWAHED
WPFDGPGGILGHAFLPNSGNPGVVHFDKNEHWSASDTGYNLFLVATHEIGHSLGLQH
GNQSSIMYPTYWYHDPRTFQLSADDIQRIQHLYGEKCSSDIP (SEQ ID NO:64)
```

FIGURE 35B

ADAM10 (NM_001110)

```
   1 gaattcgagg atccgggtac catgggcggc ggcaggccta gcagcacggg aaccgtcccc
  61 cgcgcgcatg cgcgcgcccc tgaagcgcct gggggacggg tatgggcggg aggtaggggc
 121 gcggctccgc gtgccagttg ggtgcccgcg cgtcacgtgg tgaggaagga ggcggaggtc
 181 tgagtttcga gggaggggag gagagaagag ggaacgagca agggaaggaa agcggggaaa
 241 ggaggaagga aacgaacgag ggggagggag gtccctgttt tggaggagct aggagcgttg
 301 ccggcccctg aagtggagcg agagggaggt gcttcgccgt ttctcctgcc aggggaggtc
 361 ccggcttccc gtggaggctc cggaccaagc cccttcagct tctccctccg gatcgatgtg
 421 ctgctgttaa cccgtgagga ggcggcggcg gcggcagcgg cagcggaaga tggtgttgct
 481 gagagtgtta attctgctcc tctcctgggc ggcggggatg ggaggtcagt atgggaatcc
 541 tttaaataaa tatatcagac attatgaagg attatcttac aatgtggatt cattacacca
 601 aaaacaccag cgtgccaaaa gagcagtctc acatgaagac caatttttac gtctagattt
 661 ccatgcccat ggaagacatt tcaacctacg aatgaagagg gacacttccc ttttcagtga
 721 tgaatttaaa gtagaaacat caaataaagt acttgattat gatacctctc atatttacac
 781 tggacatatt tatggtgaag aaggaagttt tagccatggg tctgttattg atggaagatt
 841 tgaaggattc atccagactc gtggtggcac attttatgtt gagccagcag agagatatat
 901 taaagaccga actctgccat ttcactctgt catttatcat gaagatgata ttaactatcc
 961 ccataaatac ggtcctcagg ggggctgtgc agatcattca gtatttgaaa gaatgaggaa
1021 ataccagatg actggtgtag aggaagtaac acagatacct caagaagaac atgctgctaa
1081 tggtccagaa cttctgagga aaaaacgtac aacttcagct gaaaaaaata cttgtcagct
1141 ttatattcag actgatcatt tgttctttaa atattacgga acacgagaag ctgtgattgc
1201 ccagatatcc agtcatgtta aagcgattga tacaatttac cagaccacag acttctccgg
1261 aatccgtaac atcagtttca tggtgaaacg cataagaatc aatacaactg ctgatgagaa
1321 ggaccctaca aatcctttcc gtttcccaaa tattggtgtg gagaagtttc tggaattgaa
1381 ttctgagcag aatcatgatg actactgttt ggcctatgtc ttcacagacc gagattttga
1441 tgatggcgta cttggtctgg cttgggttgg agcaccttca ggaagctctg gaggaatatg
1501 tgaaaaaagt aaactctatt cagatggtaa gaagaagtcc ttaaacactg gaattattac
1561 tgttcagaac tatgggtctc atgtacctcc caaagtctct cacattactt ttgctcacga
1621 agttggacat aactttggat ccccacatga ttctggaaca gagtgcacac caggagaatc
1681 taagaatttg ggtcaaaaag aaaatggcaa ttacatcatg tatgcaagag caacatctgg
1741 ggacaaactt aacaacaata aattctcact ctgtagtatt agaaatataa gccaagttct
1801 tgagaagaag agaaacaact gttttgttga atctggccaa cctatttgtg gaaatggaat
1861 ggtagaacaa ggtgaagaat gtgattgtgg ctatagtgac cagtgtaaag atgaatgctg
1921 cttcgatgca aatcaaccag agggaagaaa atgcaaactg aaacctggga aacagtgcag
1981 tccaagtcaa ggtccttgtt gtacagcaca gtgtgcattc aagtcaaagt ctgagaagtg
2041 tcgggatgat tcagactgtg caagggaagg aatatgtaat ggcttcacag ctctctgccc
2101 agcatctgac cctaaaccaa acttcacaga ctgtaatagg catacacaag tgtgcattaa
2161 tgggcaatgt gcaggttcta tctgtgagaa atatggctta gaggagtgta cgtgtgccag
2221 ttctgatggc aaagatgata aagaattatg ccatgtatgc tgtatgaaga aaatggaccc
2281 atcaacttgt gccagtacag ggtctgtgca gtggagtagg cacttcagtg gtcgaaccat
2341 caccctgcaa cctggatccc cttgcaacga ttttagaggt tactgtgatg ttttcatgcg
2401 gtgcagatta gtagatgctg atggtcctct agctaggctt aaaaaagcaa tttttagtcc
2461 agagctctat gaaaacattg ctgaatggat tgtggctcat tggtgggcag tattacttat
2521 gggaattgct ctgatcatgc taatggctgg atttattaag atatgcagtg ttcatactcc
2581 aagtagtaat ccaaagttgc ctcctcctaa accacttcca ggcactttaa agaggaggag
2641 acctccacag cccattcagc aaccccagcg tcagcggccc cgagagagtt atcaaatggg
2701 acacatgaga cgctaactgc agcttttgcc ttggttcttc ctagtgccta caatgggaaa
2761 acttcactcc aaagagaaac ctattaagtc atcatctcca aactaaaccc tcacaagtaa
2821 cagttgaaga aaaaatggca agagatcata tcctcagacc aggtggaatt acttaaattt
2881 taaagcctga aaattccaat ttgggggtgg gaggtggaaa aggaacccaa ttttcttatg
2941 aacagatatt tttaacttaa tggcacaaag tcttagaata ttattatgtg ccccgtgttc
3001 cctgttcttc gttgctgcat tttcttcact tgcaggcaaa cttggctctc aataaacttt
3061 taccacaaat tgaaataaat atattttttt caactgccaa tcaaggctag gaggctcgac
3121 cacctcaaca ttggagacat cacttgccaa tgtacatacc ttgttatatg cagacatgta
3181 tttcttacgt acactgtact tctgtgtgca attgtaaaca gaaattgcaa tatggatgtt
3241 tctttgtatt ataaaatttt tccgctctta attaaaaatt actgtttaat tgacatactc
3301 aggataacag agaatggtgg tattcagtgg tccaggattc tgtaatgctt tacacaggca
3361 gttttgaaat gaaaatcaat ttaccccatg gtacccggat cctcgaattc (SEQ ID
NO:65)
```

FIGURE 36A

ADAM10 (NM_001110)

VLLRVLILLLSWAAGMGGQYGNPLNKYIRHYEGLSYNVDSLHQ
HQRAKRAVSHEDQFLRLDFHAHGRHFNLRMKRDTSLFSDEFKVETSNKVLDYDTSHI
TGHIYGEEGSFSHGSVIDGRFEGFIQTRGGTFYVEPAERYIKDRTLPFHSVIYHEDD
NYPHKYGPQGGCADHSVFERMRKYQMTGVEEVTQIPQEEHAANGPELLRKKRTTSAE
NTCQLYIQTDHLFFKYYGTREAVIAQISSHVKAIDTIYQTTDFSGIRNISFMVKRIR
NTTADEKDPTNPFRFPNIGVEKFLELNSEQNHDDYCLAYVFTDRDFDDGVLGLAWVG
PSGSSGGICEKSKLYSDGKKKSLNTGIITVQNYGSHVPPKVSHITFAHEVGHNFGSP
DSGTECTPGESKNLGQKENGNYIMYARATSGDKLNNNKFSLCSIRNISQVLEKKRNN
FVESGQPICGNGMVEQGEECDCGYSDQCKDECCFDANQPEGRKCKLKPGKQCSPSQG
CCTAQCAFKSKSEKCRDDSDCAREGICNGFTALCPASDPKPNFTDCNRHTQVCINGQ
AGSICEKYGLEECTCASSDGKDDKELCHVCCMKKMDPSTCASTGSVQWSRHFSGRTI
LQPGSPCNDFRGYCDVFMRCRLVDADGPLARLKKAIFSPELYENIAEWIVAHWWAVL
MGIALIMLMAGFIKICSVHTPSSNPKLPPPKPLPGTLKRRRPPQPIQQPQRQRPRES
QMGHMRR (SEQ ID NO:66)

FIGURE 36B

ADAM1 (XM_132370)

1 cttgggtggg cagtgcaagc caactgcagt cagcaagtgt gcgggcttaa gagttcttcc
61 agagcccact tccatttttct ttgttgcttt aactagagtc accagtctgt cttcattttt
121 atggtgagac cattgggaga actaacttag attttaggct ctaatatagt tctgtggtaa
181 aaataagatc atgtaacact tatgctttag aaatttccat agagaaggat catgtcttaa
241 agccaaaatt tatttggtag acacaaggat acgggaaagt agaacatcta aatactgtgt
301 gtgtgtgcgt gtgcgtgtgc gtgtgtgtgt acaccagtga aaggaatcag gcagtctaag
361 agaactagct atccatccag catgaccact gtaagaatga ggaatgaggc aggacaacag
421 agaactctta attgttcaga gaacccagag aactttgtcc cctcccccga aaccctgcag
481 aatgttgagt ctgaaagtat gagctggtta acatgtcagg ggcccatgac ctgtggagga
541 ggaaagatga tgtgacaagc acagaaccgg ctgagccact gtagatgcag ggctcatctc
601 catgaatgtc aaaggaactt aagcaacact gaagctcctc cacttgaaag aagcccctgt
661 gctgcacata tccaccaagg ccaggagaaa gaaaggagag agacacagcc tgagaccgca
721 cagtttcttg ggaagctccc cagtaaggca cgggcacagg tctgggtgcc tgggtctggg
781 aaaagcagag agcactgccg ctgatggaca gagatcctcc atcatcagca gtttgttgga
841 gccatgtcag tggcagcagc ggggagaggg tttgcctcca gtctgtcttc cccacagatc
901 aggcgaatag ccttaaaaga agctaagcta acacctcaca tctgggcggc actgcactgg
961 aacttgggac tgagactagt gccatctgtc agagtaggga ttttggtgct actgattttt
1021 ctcccgagca cgttctgtga cattggatct gtatataatt cttcctatga aactgtcatc
1081 cctgagagac tgccaggcaa ggggggggaaa gaccctggag ggaaggtgtc ctacatgcta
1141 ttgatgcaag gccaaaagca gctgcttcac ctcgaggtaa agggacacta ccctgagaat
1201 aacttcccag tctacagtta ccacaatggc atcctgaggc aagaaatgcc tctcctctcc
1261 caggactgcc actatgaagg ctacatggaa ggggtgccag gctcctttgt ttctgtcaac
1321 atctgttcag gcctcagggg ggtcttgatt aaagaggaaa catcctatgg cattgagccc
1381 atgctctctt ccaaaaactt tgaacatgtc ctctacacca tggagcatca gcctgtggtc
1441 tcctgcagtg tcactcccaa agacagccct ggggacacca gccatccacc aaggagcagg
1501 aagcccgatg acctactggt tctgactgac tggtggtcac acaccaagta tgtggagatg
1561 tttgtggtgg tcaaccacca gcggttccag atgtggggca gtaacatcaa cgagacggtc
1621 caggcagtaa tggacatcat tgctctggcc aacagcttca ctaggggggat aaacacagag
1681 gtggtgctgg tgggcctgga aatctggaca gaggggggacc cgatagaggt cccagtggac
1741 ctgcagacca cactcaggaa tttcaacttc tggagacagg agaaactcgt gggccgggtc
1801 aggcacgatg tggcacactt gatcgtcggg catcgcccag gagagaacga gggccaggcg
1861 tttctccgtg gtgcctgttc gggtgagttt gcggcggccg tggaggcctt ccatcatgaa
1921 gatgtcctcc tgttcgcggc tctcatggcc cacgagctcg ggcacaacct gggtatccag
1981 cacgaccacc cgacctgcac ctgtggtccc aagcacttct gcctcatggg tgagaagatc
2041 ggtaaggaca gtggcttcag caactgcagc tctgaccact tcctccgttt cctccatgac
2101 cacagagggg cgtgcctgct tgatgagcct gggcgccaga gccgcatgcg cagagctgcc
2161 aattgtggga atggtgtggt ggaggacttg gaggagtgtg actgcggcag tgactgtgac
2221 agtcacccgt gctgttcgcc aacatgtacg cttaaggagg gtgcgcagtg cagtgaggga
2281 ctctgctgct acaactgtac attcaagaag aaagggagct tatgccgtcc tgctgaggat
2341 gtgtgtgacc ttcccgagta ttgtgacggc agtactcagg aatgccctgc aaacagctac
2401 atgcaggatg gcacacagtg tgataggatt tattactgct tgggggttg gtgtaagaac
2461 cctgataaac aatgttcaag gatctatggg tatcctgcaa gatctgcccc tgaggaatgt
2521 tacatttcag ttaatactaa ggcgaaccgg tttggaaact gtggccatcc cacctccgct
2581 aacttcagat atgaaacatg ttccgatgag gatgtatttt gtgggaaact ggtgtgtaca
2641 gatgttagat acctgcccaa agtcaaaccc ctacactcac tcctccaggt tccttatgga
2701 gaggactggt gttggagtat ggatgcctat aacatcacag atgtcccgga tgacggagat
2761 gtacagagcg gcaccttctg tgccccaaac aaagtctgca tggagtatat ctgcactggt
2821 cgtggggtgc tccagtacaa ctgtgagcca caggaaatgt gtcacgggaa tggagtgtgc
2881 aacaatttca agcactgtca ctgcgatgct ggcttcgccc ctcctgactg tagcagtcca
2941 ggaaatgggg ggagtgtgga cagtggtcct gttggtaagc ccgctgatcg acacttgagt
3001 ctctcttttc tggctgaaga gagtccagat gataaaatgg aggatgaaga ggtaaacctg
3061 aaagtgatgg tgcttgtggt ccctatattt cttgtcgttt tactgtgctg tctaatgctg
3121 atcgcctacc tctggtctga agtacaagaa gtagtatctc caccgagttc atcagagtct
3181 tcgtcttcat catcctggtc agactctgac tctcagtgaa gttttattta agatcctctc
3241 atggatcatt gctatcgatg tcttgtattt gcagggcaat tttgcctaag tggattttag
3301 ggcatgctgt tcagtgtaat gtgtggtcta tatacttgtg ttgctcatct cagaaacaac
3361 tggaattata tcctgaatga tgttaaggga tctaaatgtt ctaacttgcc ctgtcagctc
3421 ctgttcataa aatagaaggc attttaaata aatataaa (SEQ ID NO:67)

FIGURE 37A

ADAM1 (XM_132370)

MSVAAAGRGFASSLSSPQIRRIALKEAKLTPHIWAALHWNLGLR
LVPSVRVGILVLLIFLPSTFCDIGSVYNSSYETVIPERLPGKGGKDPGGKVSYMLLMQ
GQKQLLHLEVKGHYPENNFPVYSYHNGILRQEMPLLSQDCHYEGYMEGVPGSFVSVNI
CSGLRGVLIKEETSYGIEPMLSSKNFEHVLYTMEHQPVVSCSVTPKDSPGDTSHPPRS
RKPDDLLVLTDWWSHTKYVEMFVVVNHQRFQMWGSNINETVQAVMDIIALANSFTRGI
NTEVVLVGLEIWTEGDPIEVPVDLQTTLRNFNFWRQEKLVGRVRHDVAHLIVGHRPGE
NEGQAFLRGACSGEFAAAVEAFHHEDVLLFAALMAHELGHNLGIQHDHPTCTCGPKHF
CLMGEKIGKDSGFSNCSSDHFLRFLHDHRGACLLDEPGRQSRMRRAANCGNGVVEDLE
ECDCGSDCDSHPCCSPTCTLKEGAQCSEGLCCYNCTFKKKGSLCRPAEDVCDLPEYCD
GSTQECPANSYMQDGTQCDRIYYCLGGWCKNPDKQCSRIYGYPARSAPEECYISVNTK
ANRFGNCGHPTSANFRYETCSDEDVFCGKLVCTDVRYLPKVKPLHSLLQVPYGEDWCW
SMDAYNITDVPDDGDVQSGTFCAPNKVCMEYICTGRGVLQYNCEPQEMCHGNGVCNNF
KHCHCDAGFAPPDCSSPGNGGSVDSGPVGKPADRHLSLSFLAEESPDDKMEDEEVNLK
VMVLVVPIFLVVLLCCLMLIAYLWSEVQEVVSPPSSSESSSSSSWSDSDSQ (SEQ ID NO:68)

FIGURE 37B

TIM1 (NM_003254)

```
  1 aggggcctta gcgtgccgca tcgccgagat ccagcgccca gagagacacc agagaaccca
 61 ccatggcccc ctttgagccc ctggcttctg gcatcctgtt gttgctgtgg ctgatagccc
121 ccagcagggc ctgcacctgt gtcccacccc acccacagac ggccttctgc aattccgacc
181 tcgtcatcag ggccaagttc gtggggacac cagaagtcaa ccagaccacc ttataccagc
241 gttatgagat caagatgacc aagatgtata aagggttcca agccttaggg gatgccgctg
301 acatccggtt cgtctacacc cccgccatgg agagtgtctg cggatacttc cacaggtccc
361 acaaccgcag cgaggagttt ctcattgctg gaaaactgca ggatggactc ttgcacatca
421 ctacctgcag tttcgtggct ccctggaaca gcctgagctt agctcagcgc cggggcttca
481 ccaagaccta cactgttggc tgtgaggaat gcacagtgtt tccctgttta tccatccgct
541 gcaaactgca gagtggcact cattgcttgt ggacggacca gctcctccaa ggctctgaaa
601 agggcttcca gtcccgtcac cttgcctgcc tgcctcggga gccagggctg tgcacctggc
661 agtccctgcg gtcccagata gcctgaatcc tgcccggagt ggaactgaag cctgcacagt
721 gtccaccctg ttcccactcc catctttctt ccggacaatg aaataaagag ttaccaccca
781 gc (SEQ ID NO:69)
```

FIGURE 38A

TIM1 (NM_003254)

```
APFEPLASGILLLLWLIAPSRACTCVPPHPQTAFCNSDLVIRA
FVGTPEVNQTTLYQRYEIKMTKMYKGFQALGDAADIRFVYTPAMESVCGYFHRSHNR
EEFLIAGKLQDGLLHITTCSFVAPWNSLSLAQRRGFTKTYTVGCEECTVFPCLSIPC
LQSGTHCLWTDQLLQGSEKGFQSRHLACLPREPGLCTWQSLRSQIA (SEQ ID NO:70)
```

FIGURE 38B

MUC1 (XM_053256)

1 cgctccacct ctcaagcagc cagcgcctgc ctgaatctgt tctgcccccc ccccacccat
61 ttcaccacca ccatgacacc gggcacccag tctcctttct tcctgctgct gctcctcaca
121 gtgcttacag ttgttacagg ttctggtcat gcaagctcta ccccaggtgg agaaaaggag
181 acttcggcta cccagagaag ttcagtgccc agctctactg agaagaatgc tgtgagtatg
241 accagcagcg tactctccag ccacagcccc ggttcaggct cctccaccac tcagggacag
301 gatgtcactc tggccccggc cacggaacca gcttcaggtt cagctgccac ctggggacag
361 gatgtcacct cggtcccagt caccaggcca gccctgggct ccaccacccc gccagcccac
421 gatgtcacct cagccccgga caacaagcgg gccccggggct ccaccgcccc cccagcccac
481 ggtgtcacct cggccccgga caccaggccg gccccgggct ccaccgcccc cccagcccat
541 ggtgtcacct cggccccgga caacaggccc gccttgggct ccaccgcccc tccagtccac
601 aatgtcacct cggcctcagg ctctgcatca ggctcagctt ctactctggt gcacaacggc
661 acctctgcca gggctaccac aaccccagcc agcaagagca ctccattctc aattcccagc
721 caccactctg atactcctac cacccttgcc agccatagca ccaagactga tgccagtagc
781 actcaccata gcacggtacc tcctctcacc tcctccaatc acagcacttc tccccagttg
841 tctactgggg tctctttctt tttcctgtct tttcacattt caaacctcca gtttaattcc
901 tctctggaag atcccagcac cgactactac caagagctgc agagagacat ttctgaaatg
961 tttttgcaga tttataaaca agggggtttt ctgggcctct ccaatattaa gttcaggcca
1021 ggatctgtgg tggtacaatt gactctggcc ttccgagaag gtaccatcaa tgtccacgac
1081 gtggagacac agttcaatca gtataaaacg gaagcagcct ctcgatataa cctgacgatc
1141 tcagacgtca gcgtgagtga tgtgccattt cctttctctg cccagtctgg ggctggggtg
1201 ccaggctggg gcatcgcgct gctggtgctg gtctgtgttc tggttgcgct ggccattgtc
1261 tatctcattg ccttggctgt ctgtcagtgc cgccgaaaga actacgggca gctggacatc
1321 tttccagccc gggataccta ccatcctatg agcgagtacc ccacctacca cacccatggg
1381 cgctatgtgc cccctagcag taccgatcgt agcccctatg agaaggtttc tgcaggtaat
1441 ggtggcagca gcctctctta cacaaaccca gcagtggcag ccacttctgc caacttgtag
1501 gggcacgtcg cccgctgagc tgagtggcca gccagtgcca ttccactcca ctcaggttct
1561 tcagggccag agcccctgca ccctgtttgg gctggtgagc tgggagttca ggtgggctgc
1621 tcacagcctc cttcagaggc cccaccaatt tctcggacac ttctcagtgt gtggaagctc
1681 atgtgggccc ctgagggctc atgcctggga agtgttgtgg tgggggctcc caggaggact
1741 ggcccagaga gccctgagat agcggggatc ctgaactgga ctgaataaaa cgtggtctcc
1801 cactg (SEQ ID NO:71)

FIGURE 39A

MUC1 (XM_053256)

MTPGTQSPFFLLLLLTVLTVVTGSGHASSTPGGEKETSATQRSS
VPSSTEKNAVSMTSSVLSSHSPGSGSSTTQGQDVTLAPATEPASGSAATWGQDVTSVP
VTRPALGSTTPPAHDVTSAPDNKRARGSTAPPAHGVTSAPDTRPAPGSTAPPAHGVTS
APDNRPALGSTAPPVHNVTSASGSASGSASTLVHNGTSARATTTPASKSTPFSIPSHH
SDTPTTLASHSTKTDASSTHHSTVPPLTSSNHSTSPQLSTGVSFFFLSFHISNLQFNS
SLEDPSTDYYQELQRDISEMFLQIYKQGGFLGLSNIKFRPGSVVVQLTLAFREGTINV
HDVETQFNQYKTEAASRYNLTISDVSVSDVPFPFSAQSGAGVPGWGIALLVLVCVLVA
LAIVYLIALAVCQCRRKNYGQLDIFPARDTYHPMSEYPTYHTHGRYVPPSSTDRSPYE
KVSAGNGGSSLSYTNPAVAATSANL (SEQ ID NO:72)

FIGURE 39B

CEA (NM_004363)

```
   1 ctcagggcag agggaggaag gacagcagac cagacagtca cagcagcctt gacaaaacgt
  61 tcctggaact caagctcttc tccacagagg aggacagagc agacagcaga gaccatggag
 121 tctccctcgg cccctcccca cagatggtgc atcccctggc agaggctcct gctcacagcc
 181 tcacttctaa ccttctggaa cccgcccacc actgccaagc tcactattga atccacgccg
 241 ttcaatgtcg cagaggggaa ggaggtgctt ctacttgtcc acaatctgcc ccagcatctt
 301 tttggctaca gctggtacaa aggtgaaaga gtggatggca accgtcaaat tataggatat
 361 gtaataggaa ctcaacaagc taccccaggg cccgcataca gtggtcgaga gataatatac
 421 cccaatgcat ccctgctgat ccagaacatc atccagaatg acacaggatt ctacacccta
 481 cacgtcataa agtcagatct tgtgaatgaa gaagcaactg gccagttccg ggtatacccg
 541 gagctgccca agccctccat ctccagcaac aactccaaac ccgtggagga caaggatgct
 601 gtggccttca cctgtgaacc tgagactcag gacgcaacct acctgtggtg ggtaaacaat
 661 cagagcctcc cggtcagtcc caggctgcag ctgtccaatg gcaacaggac cctcactcta
 721 ttcaatgtca caagaaatga cacagcaagc tacaaatgtg aaacccagaa cccagtgagt
 781 gccaggcgca gtgattcagt catcctgaat gtcctctatg gcccggatgc ccccaccatt
 841 tcccctctaa acacatctta cagatcaggg gaaaatctga acctctcctg ccacgcagcc
 901 tctaacccac ctgcacagta ctcttggttt gtcaatggga ctttccagca atccacccaa
 961 gagctcttta tccccaacat cactgtgaat aatagtggat cctatacgtg ccaagcccat
1021 aactcagaca ctggcctcaa taggaccaca gtcacgacga tcacagtcta tgcagagcca
1081 cccaaaccct tcatcaccag caacaactcc aaccccgtgg aggatgagga tgctgtagcc
1141 ttaacctgtg aacctgagat tcagaacaca acctacctgt ggtgggtaaa taatcagagc
1201 ctcccggtca gtcccaggct gcagctgtcc aatgacaaca ggaccctcac tctactcagt
1261 gtcacaagga atgatgtagg accctatgag tgtggaatcc agaacgaatt aagtgttgac
1321 cacagcgacc cagtcatcct gaatgtcctc tatggcccag acgaccccac catttccccc
1381 tcatacacct attaccgtcc aggggtgaac ctcagcctct cctgccatgc agcctctaac
1441 ccacctgcac agtattcttg gctgattgat gggaacatcc agcaacacac acaagagctc
1501 tttatctcca acatcactga gaagaacagc ggactctata cctgccaggc caataactca
1561 gccagtggcc acagcaggac tacagtcaag acaatcacag tctctgcgga gctgcccaag
1621 ccctccatct ccagcaacaa ctccaaaccc gtggaggaca aggatgctgt ggccttcacc
1681 tgtgaacctg aggctcagaa cacaacctac ctgtggtggg taaatggtca gagcctccca
1741 gtcagtccca ggctgcagct gtccaatggc aacaggaccc tcactctatt caatgtcaca
1801 agaaatgacg caagagccta tgtatgtgga atccagaact cagtgagtgc aaaccgcagt
1861 gacccagtca ccctggatgt cctctatggg ccggacaccc ccatcatttc ccccccagac
1921 tcgtcttacc tttcgggagc gaacctcaac ctctcctgcc actcggcctc taacccatcc
1981 ccgcagtatt cttggcgtat caatgggata ccgcagcaac acacacaagt tctctttatc
2041 gccaaaatca cgccaaataa taacgggacc tatgcctgtt ttgtctctaa cttggctact
2101 ggccgcaata attccatagt caagagcatc acagtctctg catctggaac ttctcctggt
2161 ctctcagctg gggccactgt cggcatcatg attggagtgc tggttggggt tgctctgata
2221 tagcagccct ggtgtagttt cttcatttca ggaagactga cagttgtttt gcttcttcct
2281 taaagcattt gcaacagcta cagtctaaaa ttgcttcttt accaaggata tttacagaaa
2341 agactctgac cagagatcga gaccatccta gccaacatcg tgaaacccca tctctactaa
2401 aaatacaaaa atgagctggg cttggtggcg cgcacctgta gtcccagtta ctcgggaggc
2461 tgaggcagga gaatcgcttg aacccgggag gtggagattg cagtgagccc agatcgcacc
2521 actgcactcc agtctggcaa cagagcaaga ctccatctca aaaagaaaag aaaagaagac
2581 tctgacctgt actcttgaat acaagtttct gataccactg cactgtctga gaatttccaa
2641 aactttaatg aactaactga cagcttcatg aaactgtcca ccaagatcaa gcagagaaaa
2701 taattaattt catgggacta aatgaactaa tgaggattgc tgattcttta aatgtcttgt
2761 ttcccagatt tcaggaaact ttttttcttt taagctatcc actcttacag caatttgata
2821 aaatatactt ttgtgaacaa aaattgagac atttacattt tctccctatg tggtcgctcc
2881 agacttggga aactattcat gaatatttat attgtatggt aatatagtta ttgcacaagt
2941 tcaataaaaa tctgctcttt gtataacaga aaaa (SEQ ID NO:73)
```

CEA (NM_004363)

MESPSAPPHRWCIPWQRLLLTASLLTFWNPPTTAKLTIESTPFN

VAEGKEVLLLVHNLPQHLFGYSWYKGERVDGNRQIIGYVIGTQQATPGPAYSGREIIY

PNASLLIQNIIQNDTGFYTLHVIKSDLVNEEATGQFRVYPELPKPSISSNNSKPVEDK

DAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRNDTASYKCETQ

NPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGT

FQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNP

VEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYE

CGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWL

IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSN

NSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDA

RAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQ

YSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSASGTSPG

LSAGATVGIMIGVLVGVALI (SEQ ID NO:74)

FIGURE 40B

NCA (NM_002483)

```
   1 ctcctctaca aagaggtgga cagagaagac agcagagacc atgggacccc cctcagcccc
  61 tccctgcaga ttgcatgtcc cctggaagga ggtcctgctc acagcctcac ttctaacctt
 121 ctggaaccca cccaccactg ccaagctcac tattgaatcc acgccattca atgtcgcaga
 181 ggggaaggag gttcttctac tcgcccacaa cctgccccag aatcgtattg gttacagctg
 241 gtacaaaggc gaaagagtgg atggcaacag tctaattgta ggatatgtaa taggaactca
 301 acaagctacc ccagggcccg catacagtgg tcgagagaca atatacccca atgcatccct
 361 gctgatccag aacgtcaccc agaatgacac aggattctat accctacaag tcataaagtc
 421 agatcttgtg aatgaagaag caaccggaca gttccatgta tacccggagc tgcccaagcc
 481 ctccatctcc agcaacaact ccaaccccgt ggaggacaag gatgctgtgg ccttcacctg
 541 tgaacctgag gttcagaaca caacctacct gtggtgggta aatggtcaga gcctcccggt
 601 cagtcccagg ctgcagctgt ccaatggcaa catgaccctc actctactca gcgtcaaaag
 661 gaacgatgca ggatcctatg aatgtgaaat acagaaccca gcgagtgcca accgcagtga
 721 cccagtcacc ctgaatgtcc tctatggccc agatgtcccc accatttccc cctcaaaggc
 781 caattaccgt ccaggggaaa atctgaacct ctcctgccac gcagcctcta acccacctgc
 841 acagtactct tggtttatca atgggacgtt ccagcaatcc acacaagagc tctttatccc
 901 caacatcact gtgaataata gcggatccta tatgtgccaa gcccataact cagccactgg
 961 cctcaatagg accacagtca cgatgatcac agtctctgga agtgctcctg tcctctcagc
1021 tgtggccacc gtcggcatca cgattggagt gctggccagg gtggctctga tatagcagcc
1081 ctggtgtatt ttcgatattt caggaagact ggcagattgg accagaccct gaattcttct
1141 agctcctcca atcccatttt atcccatgga accactaaaa acaaggtctg ctctgctcct
1201 gaagccctat atgctggaga tggacaactc aatgaaaatt taaagggaaa accctcaggc
1261 ctgaggtgtg tgccactcag agacttcacc taactagaga cagtcaaact gcaaaccatg
1321 gtgagaaatt gacgacttca cactatggac agcttttccc aagatgtcaa aacaagactc
1381 ctcatcatga taaggctctt acccccttt aatttgtcct tgcttatgcc tgcctctttc
1441 gcttggcagg atgatgctgt cattagtatt tcacaagaag tagcttcaga gggtaactta
1501 acagagtgtc agatctatct tgtcaatccc aacgttttac ataaaataag agatccttta
1561 gtgcacccag tgactgacat tagcagcatc tttaacacag ccgtgtgttc aaatgtacag
1621 tggtcctttt cagagttgga cttctagact cacctgttct cactccctgt tttaattcaa
1681 cccagccatg caatgccaaa taatagaatt gctccctacc agctgaacag ggaggagtct
1741 gtgcagtttc tgacacttgt tgttgaacat ggctaaatac aatgggtatc gctgagacta
1801 agttgtagaa attaacaaat gtgctgcttg gttaaaatgg ctacactcat ctgactcatt
1861 ctttattcta ttttagttgg tttgtatctt gcctaaggtg cgtagtccaa ctcttggtat
1921 taccctccta atagtcatac tagtagtcat actccctggt gtagtgtatt ctctaaaagc
1981 tttaaatgtc tgcatgcagc cagccatcaa atagtgaatg gtctctcttt ggctggaatt
2041 acaaaactca gagaaatgtg tcatcaggag aacatcataa cccatgaagg ataaaagccc
2101 caaatggtgg taactgataa tagcactaat gctttaagat ttggtcacac tctcacctag
2161 gtgagcgcat tgagccagtg gtgctaaatg ctacatactc caactgaaat gttaaggaag
2221 aagatagatc caaaaaaaaa aaaaaaaaa (SEQ ID NO:75)
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FIGURE 41

NCA (NM_002483)

MGPPSAPPCRLHVPWKEVLLTASLLTFWNPPTTAKLTIESTPFN

VAEGKEVLLLAHNLPQNRIGYSWYKGERVDGNSLIVGYVIGTQQATPGPAYSGRETIY

PNASLLIQNVTQNDTGFYTLQVIKSDLVNEEATGQFHVYPELPKPSISSNNSNPVEDK

DAVAFTCEPEVQNTTYLWWVNGQSLPVSPRLQLSNGNMTLTLLSVKRNDAGSYECEIQ

NPASANRSDPVTLNVLYGPDVPTISPSKANYRPGENLNLSCHAASNPPAQYSWFINGT

FQQSTQELFIPNITVNNSGSYMCQAHNSATGLNRTTVTMITVSGSAPVLSAVATVGIT

IGVLARVALI (SEQ ID NO: 76)

FIGURE 41B

Follistatin (NM_006350)

```
   1 gctcctcgcc ccgcgcctgc ccccaggatg gtccgcgcga ggcaccagcc gggtgggctt
  61 tgcctcctgc tgctgctgct ctgccagttc atggaggacc gcagtgccca ggctgggaac
 121 tgctggctcc gtcaagcgaa gaacggccgc tgccaggtcc tgtacaagac cgaactgagc
 181 aaggaggagt gctgcagcac cggccggctg agcacctcgt ggaccgagga ggacgtgaat
 241 gacaacacac tcttcaagtg gatgattttc aacgggggcg cccccaactg catcccctgt
 301 aaagaaacgt gtgagaacgt ggactgtgga cctgggaaaa aatgccgaat gaacaagaag
 361 aacaaacccc gctgcgtctg cgccccggat tgttccaaca tcacctggaa gggtccagtc
 421 tgcgggctgg atgggaaaac ctaccgcaat gaatgtgcac tcctaaaggc aagatgtaaa
 481 gagcagccag aactggaagt ccagtaccaa ggcagatgta aaaagacttg tcgggatgtt
 541 ttctgtccag gcagctccac atgtgtggtg gaccagacca ataatgccta ctgtgtgacc
 601 tgtaatcgga tttgcccaga gcctgcttcc tctgagcaat atctctgtgg gaatgatgga
 661 gtcacctact ccagtgcctg ccacctgaga aaggctacct gcctgctggg cagatctatt
 721 ggattagcct atgagggaaa gtgtatcaaa gcaaagtcct gtgaagatat ccagtgcact
 781 ggtgggaaaa aatgtttatg ggatttcaag gttgggagag gccggtgttc cctctgtgat
 841 gagctgtgcc ctgacagtaa gtcggatgag cctgtctgtg ccagtgacaa tgccacttat
 901 gccagcgagt gtgccatgaa ggaagctgcc tgctcctcag gtgtgctact ggaagtaaag
 961 cactccggat cttgcaactg aatctgcccg taaaacctga gccattgatt cttcagaact
1021 ttctgcagtt tttgacttca tagattatgc tttaaaaaat ttttttaac ttattgcata
1081 acagcagatg ccaaaaacaa aaaaagcatc tcactgcaag tcacataaaa atgcaacgct
1141 gtaatatggc tgtatcagag ggctttgaaa acatacactg agctgcttct gcgctgttgt
1201 tgtccgtatt taaacaacag ctcccctgta ttcccccatc tagccatttc ggaagacacc
1261 gaggaagagg aggaagatga agaccaggac tacagctttc ctatatcttc tattctagag
1321 tggtaaactc tctataagtg ttcagtgttc acatagcctt tgtgcaaaaa aaaaaaaaaa
1381 aaaaaa (SEQ ID NO:77)
```

FIGURE 42A

Follistatin (NM_006350)

MVRARHQPGGLCLLLLLLCQFMEDRSAQAGNCWLRQAKNGRCQV

LYKTELSKEECCSTGRLSTSWTEEDVNDNTLFKWMIFNGGAPNCIPCKETCENVDCGP

GKKCRMNKKNKPRCVCAPDCSNITWKGPVCGLDGKTYRNECALLKARCKEQPELEVQY

QGRCKKTCRDVFCPGSSTCVVDQTNNAYCVTCNRICPEPASSEQYLCGNDGVTYSSAC

HLRKATCLLGRSIGLAYEGKCIKAKSCEDIQCTGGKKCLWDFKVGRGRCSLCDELCPD

SKSDEPVCASDNATYASECAMKEAACSSGVLLEVKHSGSCN (SEQ ID NO: 78)

FIGURE 42B

Claudin 1 (NM_021101)

```
   1 gagcaaccgc agcttctagt atccagactc cagcgccgcc ccgggcgcgg accccaaccc
  61 cgacccagag cttctccagc ggcggcgcag cgagcagggc tccccgcctt aacttcctcc
 121 gcgggggccca gccaccttcg ggagtccggg ttgcccacct gcaaactctc cgccttctgc
 181 acctgccacc cctgagccag cgcgggcgcc cgagcgagtc atggccaacg cggggctgca
 241 gctgttgggc ttcattctcg ccttcctggg atggatcggc gccatcgtca gcactgccct
 301 gccccagtgg aggatttact cctatgccgg cgacaacatc gtgaccgccc aggccatgta
 361 cgaggggctg tggatgtcct gcgtgtcgca gagcaccggg cagatccagt gcaaagtctt
 421 tgactccttg ctgaatctga gcagcacatt gcaagcaacc cgtgccttga tggtggttgg
 481 catcctcctg ggagtgatag caatctttgt ggccaccgtt ggcatgaagt gtatgaagtg
 541 cttggaagac gatgaggtgc agaagatgag gatggctgtc attgggggtg cgatatttct
 601 tcttgcaggt ctggctattt tagttgccac agcatggtat ggcaatagaa tcgttcaaga
 661 attctatgac cctatgaccc cagtcaatgc caggtacgaa tttggtcagg ctctcttcac
 721 tggctgggct gctgcttctc tctgccttct gggaggtgcc ctactttgct gttcctgtcc
 781 ccgaaaaaca acctcttacc caacaccaag gccctatcca aaacctgcac cttccagcgg
 841 gaaagactac gtgtgacaca gaggcaaaag gagaaaatca tgttgaaaca aaccgaaaat
 901 ggacattgag atactatcat taacattagg accttagaat tttgggtatt gtaatctgaa
 961 gtatggtatt acaaaacaaa caaacaaaca aaaaacccat gtgttaaaat actcagtgct
1021 aaacatggct taatcttatt ttatcttctt tcctcaatat aggagggaag atttttccat
1081 ttgtattact gcttcccatt gagtaatcat actcaattgg gggaaggggt gctccttaaa
1141 tatatataga tatgtatata tacatgtttt tctattaaaa atagacagta aaatactatt
1201 ctcattatgt tgatactagc atacttaaaa tatctctaaa ataggtaaat gtatttaatt
1261 ccatattgat gaagatgttt attggtatat tttctttttc gtctatatat acatatgtaa
1321 cagtcaaata tcatttactc ttcttcatta gctttgggtg cctttgccac aagacctagc
1381 ctaatttacc aaggatgaat tctttcaatt cttcatgcgt gccctttttca tatacttatt
1441 ttatttttta ccataatctt atagcacttg catcgttatt aagcccttat ttgttttgtg
1501 tttcattggt ctctatctcc tgaatctaac acatttcata gcctacattt tagtttctaa
1561 agccaagaag aatttattac aaatcagaac tttggaggca aatctttctg catgaccaaa
1621 gtgataaatt cctgttgacc ttcccacaca atccctgtac tctgacccat agcactcttg
1681 tttgctttga aaatatttgt ccaattgagt agctgcatgc tgttccccca ggtgttgtaa
1741 cacaacttta ttgattgaat ttttaagcta cttattcata gttttatatc cccctaaact
1801 acctttttgt tccccattcc ttaattgtat tgttttccca agtgtaatta tcatgcgttt
1861 tatatcttcc taataaggtg tggtctgttt gtctgaacaa agtgctagac tttctggagt
1921 gataatctgg tgacaaatat tctctctgta gctgtaagca agtcacttaa tctttctacc
1981 tctttttttct atctgccaaa ttgagataat gatacttaac cagttagaag aggtagtgtg
2041 aatattaatt agtttatatt actctcattc tttgaacatg aactatgcct atgtagtgtc
2101 tttatttgct cagctggctg agacactgaa gaagtcactg aacaaaacct acacacgtac
2161 cttcatgtga ttcactgcct tcctctctct accagtctat ttccactgaa caaaacctac
2221 acacatacct tcatgtggtt cagtgccttc ctctctctac cagtctattt ccactgaaca
2281 aaacctacgc acataccttc atgtggctca gtgccttcct ctctctacca gtctatttcc
2341 attctttcag ctgtgtctga catgtttgtg ctctgttcca ttttaacaac tgctcttact
2401 tttccagtct gtacagaatg ctatttcact tgagcaagat gatgtaatgg aaagggtgtt
2461 ggcattggtg tctggagacc tggatttgag tcttggtgct atcaatcacc gtctgtgttt
2521 gagcaaggca tttggctgct gtaagcttat tgcttcatct gtaagcggtg gtttgtaatt
2581 cctgatcttc ccacctcaca gtgatgttgt ggggatccag tgagatagaa tacatgtaag
2641 tgtggttttg taatttaaaa agtgctatac taagggaaag aattgaggaa ttaactgcat
2701 acgttttggt gttgcttttc aaatgtttga aaacaaaaaa aatgttaaga aatgggtttc
2761 ttgccttaac cagtctctca agtgatgaga cagtgaagta aaattgagtg cactaaacaa
2821 ataagattct gaggaagtct tatcttctgc agtgagtatg gcccgatgct ttctgtggct
2881 aaacagatgt aatgggaaga aataaaagcc tacgtgttgg taaatccaac agcaagggag
2941 atttttgaat cataataact cataaggtgc tatctgttca gtgatgccct cagagctctt
3001 gctgttagct ggcagctgac gctgctagga tagttagttt ggaaatggta cttcataata
3061 aactacacaa ggaaagtcag ccactgtgtc ttatgaggaa ttggacctaa taaatttag
3121 tgtgccttcc aaacctgaga atatatgctt ttggaagtta aaatttaaat ggcttttgcc
3181 acatacatag atcttcatga tgtgtgagtg taattccatg tggatatcag ttaccaaaca
3241 ttacaaaaaa attttatggc ccaaaatgac caacgaaatt gttacaatag aatttatcca
3301 attttgatct ttttatattc ttctaccaca cctggaaaca gaccaataga cattttgggg
3361 ttttataata ggaatttgta taaagcatta ctctttttca ataaattgtt ttttaattta
3421 aaaaaaggaa aaaaaaaaaa aaaaa (SEQ ID NO:79)
```

FIGURE 43A

Claudin 1 (NM_021101)

MANAGLQLLGFILAFLGWIGAIVSTALPQWRIYSYAGDNIVTAQ

AMYEGLWMSCVSQSTGQIQCKVFDSLLNLSSTLQATRALMVVGILLGVIAIFVATVGM

KCMKCLEDDEVQKMRMAVIGGAIFLLAGLAILVATAWYGNRIVQEFYDPMTPVNARYE

FGQALFTGWAAASLCLLGGALLCCSCPRKTTSYPTPRPYPKPAPSSGKDYV (SEQ ID NO:80)

FIGURE 43B

Claudin 14 (NM_012130)

```
   1 gtttgcttca ccttctgcca ggattgtaag tttcctgagg cctccccagt cctgcggaac
  61 tggctccggc tggcacctga ggagcggcgt gaccccgagg gcccagggag ctgcccggct
 121 ggcctaggca ggcagccgca ccatggccag cacggccgtg cagcttctgg gcttcctgct
 181 cagcttcctg ggcatggtgg gcacgttgat caccaccatc ctgccgcact ggcggaggac
 241 agcgcacgtg ggcaccaaca tcctcacggc cgtgtcctac ctgaaagggc tctggatgga
 301 gtgtgtgtgg cacagcacag gcatctacca gtgccagatc taccgatccc tgctggcgct
 361 gccccaagac ctccaggctg cccgcgccct catggtcatc tcctgcctgc tctcgggcat
 421 agcctgcgcc tgcgccgtca tcgggatgaa gtgcacgcgc tgcgccaagg gcacacccgc
 481 caagaccacc tttgccatcc tcggcggcac cctcttcatc ctggccggcc tcctgtgcat
 541 ggtggccgtc tcctggacca ccaacgacgt ggtgcagaac ttctacaacc cgctgctgcc
 601 cagcggcatg aagtttgaga ttggccaggc cctgtacctg ggcttcatct cctcgtccct
 661 ctcgctcatt ggtggcaccc tgctttgcct gtcctgccag gacgaggcac cctacaggcc
 721 ctaccaggcc ccgcccaggg ccaccacgac cactgcaaac accgcacctg cctaccagcc
 781 accagctgcc tacaaagaca atcgggcccc ctcagtgacc tcggccacgc acagcgggta
 841 caggctgaac gactacgtgt gagtccccac agcctgcttc tcccctgggc tgctgtgggc
 901 tgggtccccg gcgggactgt caatggaggc aggggttcca gcacaaagtt tacttctggg
 961 caatttttgt atccaaggaa ataatgtgaa tgcgaggaaa tgtctttaga gcacagggac
1021 agaggggggaa ataagaggag gagaaagctc tctataccaa agactgaaaa aaaaaatcct
1081 gtctgttttt gtatttatta tatatattta tgtgggtgat ttgataacaa gtttaatata
1141 aagtgacttg ggagtttggt cagtggggtt ggtttgtgat ccaggaataa accttgcgga
1201 tgtggctgtt tatgaaaaaa aaaaaaaaaa aaa (SEQ ID NO:81)
```

FIGURE 44A

Claudin 14 (NM_012130)

MASTAVQLLGFLLSFLGMVGTLITTILPHWRRTAHVGTNILTAV

SYLKGLWMECVWHSTGIYQCQIYRSLLALPQDLQAARALMVISCLLSGIACACAVIGM

KCTRCAKGTPAKTTFAILGGTLFILAGLLCMVAVSWTTNDVVQNFYNPLLPSGMKFEI

GQALYLGFISSSLSLIGGTLLCLSCQDEAPYRPYQAPPRATTTTANTAPAYQPPAAYK

DNRAPSVTSATHSGYRLNDYV (SEQ ID NO:82)

FIGURE 44B

Tenascin-R (NM_003285)

```
   1 ccttggtttc cgttgcagat tcccacaact ccatgctgtg tgctgcaggc tggtcctgaa
  61 cccagatctc tggctgagag gatgggggca gatggggaaa cagtggttct gaagaacatg
 121 ctcattggcg tcaacctgat ccttctgggc tccatgatca agccttcaga gtgtcagctg
 181 gaggtcacca cagaaagggt ccagagacag tcagtggagg aggagggagg cattgccaac
 241 tacaacacgt ccagcaaaga gcagcctgtg gtcttcaacc acgtgtacaa cattaacgtg
 301 cccttggaca acctctgctc ctcagggcta gaggcctctg ctgagcagga ggtgagtgca
 361 gaagacgaga ctctggcaga gtacatgggc cagacctcag accacgagag ccaggtcacc
 421 tttacacaca ggatcaactt ccccaaaaag gcctgtccat gtgccagttc agcccaggtg
 481 ctgcaggagc tgctgagccg gatcgagatg ctggagaggg aggtgtcggt gctgcgagac
 541 cagtgcaacg ccaactgctg ccaagaaagt gctgccacag gacaactgga ctatatccct
 601 cactgcagtg gccacggcaa ctttagcttt gagtcctgtg gctgcatctg caacgaaggc
 661 tggtttggca agaattgctc ggagccctac tgcccgctgg gttgctccag ccgggggggtg
 721 tgtgtggatg gccagtgcat ctgtgacagc gaatacagcg gggatgactg ttccgaactc
 781 cggtgcccaa cagactgcag ctcccggggg ctctgcgtgg acggggagtg tgtctgtgaa
 841 gagccctaca ctggcgagga ctgcagggaa ctgaggtgcc ctggggactg ttcggggaag
 901 gggagatgtg ccaacggtac ctgtttatgc gaggagggct acgttggtga ggactgcggc
 961 cagcggcagt gtctgaatgc ctgcagtggg cgaggacaat gtgaggaggg gctctgcgtc
1021 tgtgaagagg gctaccaggg ccctgactgc tcagcagttg cccctccaga ggacttgcga
1081 gtggctggta tcagcgacag gtccattgag ctggaatggg acgggccgat ggcagtgacg
1141 gaatatgtga tctcttacca gccgacggcc ctgggggcc tccagctcca gcagcgggtg
1201 cctggagatt ggagtggtgt caccatcacg gagctggagc caggtctcac ctacaacatc
1261 agcgtctacg ctgtcattag caacatcctc agccttccca tcactgccaa ggtggccacc
1321 catctctcca ctcctcaagg gctacaattt aagacgatca cagagaccac cgtggaggtg
1381 cagtgggagc ccttctcatt ttccttcgat gggtgggaaa tcagcttcat tccaaagaac
1441 aatgaagggg gagtgattgc tcaggtcccc agcgatgtta cgtcctttaa ccagacagga
1501 ctaaagcctg gggaggaata cattgtcaat gtggtggctc tgaaagaaca ggcccgcagc
1561 ccccctacct cggccagcgt ctccacagtc attgacggcc ccacgcagat cctggttcgc
1621 gatgtctcgg acaccgtggc ttttgtggag tggattcccc ctcgagccaa agtcgatttc
1681 attcttttga aatatggcct ggtgggcggg gaaggtggga ggaccacctt ccggctgcag
1741 cctcccctga gccaatactc agtgcaggcc ctgcggcctg gctcccgata cgaggtgtca
1801 gtcagtgccg tccgagggac caacgagagc gattctgcca ccactcagtt cacaacagag
1861 atcgatgccc ccaagaactt gcgagttggt tctcgcacag caaccagcct tgacctcgag
1921 tgggataaca gtgaagccga agttcaggag tacaaggttg tgtacagcac cctggcgggt
1981 gagcaatatc atgaggtact ggtccccagg ggcattggtc caaccaccag ggccaccctg
2041 acagatctgg tacctggcac tgagtatgga gttggaatat ctgccgtcat gaactcacag
2101 caaagcgtgc cagccaccat gaatgccagg actgaacttg acagtccccg agacctcatg
2161 gtgacagcct cctcggagac ctccatctcc ctcatctgga ccaaggccag tggccccatt
2221 gaccactacc gaattacctt taccccatcc tctgggattg cctcagaagt caccgtaccc
2281 aaggacagga cctcatacac actaacagat ctagagcctg gggcagagta catcatttcc
2341 gtcactgctg agaggggtcg gcagcagagc ttggagtcca ctgtggatgc tttcacaggc
2401 ttccgtccca tctctcatct gcacttttct catgtgacct cctccagtgt gaacatcact
2461 tggagtgatc catctccccc agcagacaga ctcattctta actacagccc cagggatgag
2521 gaggaagaga tgatggaggt ctccctggat gccaccaaga ggcatgctgt cctgatgggc
2581 ctgcaaccag ccacagagta tattgtgaac cttgtggctg tccatggcac agtgacctct
2641 gagcccattg tgggctccat caccacagga attgatcccc caaaagacat cacaattagc
2701 aatgtgacca aggactcagt gatggtctcc tggagccctc ctgttgcatc tttcgattac
2761 taccgagtat catatcgacc cacccaagtg ggacgactag acagctcagt ggtgcccaac
2821 actgtgacag aattcaccat caccagactg aacccagcta ccgaatacga aatcagcctc
2881 aacagcgtgc ggggcaggga ggaaagcgag cgcatctgta ctcttgtgca cacagccatg
2941 gacaaccctg tggatctgat tgctaccaat atcactccaa cagaagccct gctgcagtgg
3001 aaggcaccag tgggtgaggt ggagaactac gtcattgttc ttacacactt tgcagtcgct
3061 ggagagacca tccttgttga cggagtcagt gaggaatttc ggcttgttga cctgcttcct
3121 agcacccact atactgccac catgtatgcc accaatggac ctctcaccag tggcaccatc
3181 agcaccaact tttctactct cctggaccct ccggcaaacc tgacagccag tgaagtcacc
3241 agacaaagtg ccctgatctc ctggcagcct cccagggcag agattgaaaa ttatgtcttg
3301 acctacaaat ccaccgacgg aagccgcaag gagctgattg tggatgcaga agacacctgg
3361 attcgactgg agggcctgtt ggagaacaca gactacacgg tgctcctgca ggcagcacag
```

FIGURE 45A

3421 gacaccacgt ggagcagcat cacctccacc gctttcacca caggaggccg ggtgttccct
3481 catccccaag actgtgccca gcatttgatg aatggagaca ctttgagtgg ggtttacccc
3541 atcttcctca atggggagct gagccagaaa ttacaagtgt actgtgatat gaccaccgac
3601 gggggcggct ggattgtatt ccagaggcgg cagaatggcc aaactgattt tttccggaaa
3661 tgggctgatt accgtgttgg cttcgggaac gtggaggatg agttctggct ggggctggac
3721 aatatacaca ggatcacatc ccagggccgc tatgagctgc gcgtggacat gcgggatggc
3781 caggaggccg ccttcgcctc ctacgacagg ttctctgtcg aggacagcag aaacctgtac
3841 aaactccgca taggaagcta caacggcact gcgggggact ccctcagcta tcatcaagga
3901 cgccctttct ccacagagga tagagacaat gatgttgcag tgactaactg tgccatgtcg
3961 tacaagggag catggtggta taagaactgc caccggacca acctcaatgg gaagtacggg
4021 gagtccaggc acagtcaggg catcaactgg taccattgga aaggccatga gttctccatc
4081 cctttgtgg aaatgaagat gcgcccctac aaccaccgtc tcatggcagg gagaaaacgg
4141 cagtccttac agttctgagc agtgggcggc tgcaagccaa ccaatatttt ctgtcatttg
4201 tttgtatttt ataatatgaa acaaggggg agggtaatag caatgtgttt tgcaacatat
4261 taagagtatg tgaaggaagc agggatgtcg caggaatccg ctggctaaca tctgctcttg
4321 gtttctgctg ccctggagcc tgaccctcag tctccattct ccctcctacc caggcctcct
4381 caaccttcac ctcctttccc accaaggagg agaagtagga agttttctta aagggccaat
4441 tcaaagccaa gtcgtggggt gcagattgtt atggtgacag gcacacacat ttttctaccc
4501 ttcttctgag atgtcctctg ccttccaggt atttgtgatt ttgtcacagc ctgacatggc
4561 caggttctca cactggccca gagaaaagag cctcagcaag agagttttgc caacaattcc
4621 ccttaaaagg aaacagatca actacaccgc atcccaacaa cccaggttct tttccttcct
4681 tccttccttc ctcccttcct tctttcctgc cttccc (SEQ ID NO:83)

FIGURE 45B

Tenascin-R (NM_003285)

MGADGETVVLKNMLIGVNLILLGSMIKPSECQLEVTTERVQRQS

VEEEGGIANYNTSSKEQPVVFNHVYNINVPLDNLCSSGLEASAEQEVSAEDETLAEYM

GQTSDHESQVTFTHRINFPKKACPCASSAQVLQELLSRIEMLEREVSVLRDQCNANCC

QESAATGQLDYIPHCSGHGNFSFESCGCICNEGWFGKNCSEPYCPLGCSSRGVCVDGQ

CICDSEYSGDDCSELRCPTDCSSRGLCVDGECVCEEPYTGEDCRELRCPGDCSGKGRC

ANGTCLCEEGYVGEDCGQRQCLNACSGRGQCEEGLCVCEEGYQGPDCSAVAPPEDLRV

AGISDRSIELEWDGPMAVTEYVISYQPTALGGLQLQQRVPGDWSGVTITELEPGLTYN

ISVYAVISNILSLPITAKVATHLSTPQGLQFKTITETTVEVQWEPFSFSFDGWEISFI

PKNNEGGVIAQVPSDVTSFNQTGLKPGEEYIVNVVALKEQARSPPTSASVSTVIDGPT

QILVRDVSDTVAFVEWIPPRAKVDFILLKYGLVGGEGGRTTFRLQPPLSQYSVQALRP

GSRYEVSVSAVRGTNESDSATTQFTTEIDAPKNLRVGSRTATSLDLEWDNSEAEVQEY

KVVYSTLAGEQYHEVLVPRGIGPTTRATLTDLVPGTEYGVGISAVMNSQQSVPATMNA

RTELDSPRDLMVTASSETSISLIWTKASGPIDHYRITFTPSSGIASEVTVPKDRTSYT

LTDLEPGAEYIISVTAERGRQQSLESTVDAFTGFRPISHLHFSHVTSSSVNITWSDPS

PPADRLILNYSPRDEEEEMMEVSLDATKRHAVLMGLQPATEYIVNLVAVHGTVTSEPI

VGSITTGIDPPKDITISNVTKDSVMVSWSPPVASFDYYRVSYRPTQVGRLDSSVVPNT

VTEFTITRLNPATEYEISLNSVRGREESERICTLVHTAMDNPVDLIATNITPTEALLQ

WKAPVGEVENYVIVLTHFAVAGETILVDGVSEEFRLVDLLPSTHYTATMYATNGPLTS

GTISTNFSTLLDPPANLTASEVTRQSALISWQPPRAEIENYVLTYKSTDGSRKELIVD

AEDTWIRLEGLLENTDYTVLLQAAQDTTWSSITSTAFTTGGRVFPHPQDCAQHLMNGD

TLSGVYPIFLNGELSQKLQVYCDMTTDGGGWIVFQRRQNGQTDFFRKWADYRVGFGNV

EDEFWLGLDNIHRITSQGRYELRVDMRDGQEAAFASYDRFSVEDSRNLYKLRIGSYNG

TAGDSLSYHQGRPFSTEDRDNDVAVTNCAMSYKGAWWYKNCHRTNLNGKYGESRHSQG

INWYHWKGHEFSIPFVEMKMRPYNHRLMAGRKRQSLQF (SEQ ID NO:84)

FIGURE 45C

CAD3 (NM-001793)

```
   1 aaaggggcaa gagctgagcg gaacaccggc ccgccgtcgc ggcagctgct tcacccctct
  61 ctctgcagcc atggggctcc ctcgtggacc tctcgcgtct ctcctccttc tccaggtttg
 121 ctggctgcag tgcgcggcct ccgagccgtg ccgggcggtc ttcagggagg ctgaagtgac
 181 cttggaggcg ggaggcgcgg agcaggagcc cggccaggcg ctggggaaag tattcatggg
 241 ctgccctggg caagagccag ctctgtttag cactgataat gatgacttca ctgtgcggaa
 301 tggcgagaca gtccaggaaa gaaggtcact gaaggaaagg aatccattga agatcttccc
 361 atccaaacgt atcttacgaa gacacaagag agattgggtg gttgctccaa tatctgtccc
 421 tgaaaatggc aagggtccct tcccccagag actgaatcag ctcaagtcta ataaagatag
 481 agacaccaag attttctaca gcatcacggg gccgggggca gacagccccc ctgagggtgt
 541 cttcgctgta gagaaggaga caggctggtt gttgttgaat aagccactgg accgggagga
 601 gattgccaag tatgagctct ttggccacgc tgtgtcagag aatggtgcct cagtggagga
 661 ccccatgaac atctccatca tcgtgaccga ccagaatgac cacaagccca agtttaccca
 721 ggacaccttc cgagggagtg tcttagaggg agtcctacca ggtacttctg tgatgcaggt
 781 gacagccacg gatgaggatg atgccatcta cacctacaat ggggtggttg cttactccat
 841 ccatagccaa gaaccaaagg acccacacga cctcatgttc accattcacc ggagcacagg
 901 caccatcagc gtcatctcca gtggcctgga ccgggaaaaa gtccctgagt acacactgac
 961 catccaggcc acagacatgg atggggacgg ctccaccacc acggcagtgg cagtagtgga
1021 gatccttgat gccaatgaca atgctcccat gtttgacccc cagaagtacg aggcccatgt
1081 gcctgagaat gcagtgggcc atgaggtgca gaggctgacg gtcactgatc tggacgcccc
1141 caactcacca gcgtggcgtg ccacctacct tatcatgggc ggtgacgacg gggaccattt
1201 taccatcacc acccaccctg agagcaacca gggcatcctg acaaccagga agggtttgga
1261 ttttgaggcc aaaaaccagc acaccctgta cgttgaagtg accaacgagg ccccttttgt
1321 gctgaagctc ccaacctcca cagccaccat agtggtccac gtggaggatg tgaatgaggc
1381 acctgtgttt gtcccaccct ccaaagtcgt tgaggtccag gagggcatcc ccactgggga
1441 gcctgtgtgt gtctacactg cagaagaccc tgacaaggag aatcaaaaga tcagctaccg
1501 catcctgaga gacccagcag ggtggctagc catggaccca gacagtgggc aggtcacagc
1561 tgtgggcacc ctcgaccgtg aggatgagca gtttgtgagg aacaacatct atgaagtcat
1621 ggtcttggcc atggacaatg gaagccctcc caccactggc acgggaaccc ttctgctaac
1681 actgattgat gtcaatgacc atggcccagt ccctgagccc cgtcagatca ccatctgcaa
1741 ccaaagccct gtgcgccagg tgctgaacat cacggacaag gacctgtctc cccacacctc
1801 ccctttccag gcccagctca cagatgactc agacatctac tggacggcag aggtcaacga
1861 ggaaggtgac acagtggtct tgtccctgaa gaagttcctg aagcaggata catatgacgt
1921 gcacctttct ctgtctgacc atggcaacaa agagcagctg acggtgatca gggccactgt
1981 gtgcgactgc catggccatg tcgaaacctg ccctggaccc tggaagggag gtttcatcct
2041 ccctgtgctg ggggctgtcc tggctctgct gttcctcctg ctggtgctgc ttttgttggt
2101 gagaaagaag cggaagatca aggagcccct cctactccca gaagatgaca cccgtgacaa
2161 cgtcttctac tatggcgaag agggggggtgg cgaagaggac caggactatg acatcaccca
2221 gctccaccga ggtctggagg ccaggccgga ggtggttctc cgcaatgacg tggcaccaac
2281 catcatcccg acacccatgt accgtcctcg gccagccaac ccagatgaaa tcggcaactt
2341 tataattgag aacctgaagg cggctaacac agaccccaca gccccgccct acgacaccct
2401 cttggtgttc gactatgagg gcagcggctc cgacgccgcg tccctgagct ccctcacctc
2461 ctccgcctcc gaccaagacc aagattacga ttatctgaac gagtggggca gccgcttcaa
2521 gaagctggca gacatgtacg gtggcgggga ggacgactag gcggcctgcc tgcagggctg
2581 gggaccaaac gtcaggccac agagcatctc caaggggtct cagttccccc ttcagctgag
2641 gacttcggag cttgtcagga agtggccgta gcaacttggc ggagacaggc tatgagtctg
2701 acgttagagt ggttgcttcc ttagcctttc aggatggagg aatgtgggca gtttgacttc
2761 agcactgaaa acctctccac ctgggccagg gttgcctcag aggccaagtt tccagaagcc
2821 tcttacctgc cgtaaaatgc tcaaccctgt gtcctgggcc tgggcctgct gtgactgacc
2881 tacagtggac tttctctctg gaatggaacc ttcttaggcc tcctggtgca acttaatttt
2941 tttttttaat gctatcttca aaacgttaga gaaagttctt caaaagtgca gcccagagct
3001 gctgggccca ctggccgtcc tgcatttctg gtttccagac cccaatgcct cccattcgga
3061 tggatctctg cgtttttata ctgagtgtgc ctaggttgcc ccttattttt tattttccct
3121 gttgcgttgc tatagatgaa gggtgaggac aatcgtgtat atgtactaga acttttttat
3181 taaagaaact tttcccagaa aaaaa (SEQ ID NO:85)
```

FIGURE 46A

CAD3 (NM-001793)

MGLPRGPLASLLLLQVCWLQCAASEPCRAVFREAEVTLEAGGAE

QEPGQALGKVFMGCPGQEPALFSTDNDDFTVRNGETVQERRSLKERNPLKIFPSKRIL

RRHKRDWVVAPISVPENGKGPFPQRLNQLKSNKDRDTKIFYSITGPGADSPPEGVFAV

EKETGWLLLNKPLDREEIAKYELFGHAVSENGASVEDPMNISIIVTDQNDHKPKFTQD

TFRGSVLEGVLPGTSVMQVTATDEDDAIYTYNGVVAYSIHSQEPKDPHDLMFTIHRST

GTISVISSGLDREKVPEYTLTIQATDMDGDGSTTTAVAVVEILDANDNAPMFDPQKYE

AHVPENAVGHEVQRLTVTDLDAPNSPAWRATYLIMGGDDGDHFTITTHPESNQGILTT

RKGLDFEAKNQHTLYVEVTNEAPFVLKLPTSTATIVVHVEDVNEAPVFVPPSKVVEVQ

EGIPTGEPVCVYTAEDPDKENQKISYRILRDPAGWLAMDPDSGQVTAVGTLDREDEQF

VRNNIYEVMVLAMDNGSPPTTGTGTLLLTLIDVNDHGPVPEPRQITICNQSPVRQVLN

ITDKDLSPHTSPFQAQLTDDSDIYWTAEVNEEGDTVVLSLKKFLKQDTYDVHLSLSDH

GNKEQLTVIRATVCDCHGHVETCPGPWKGGFILPVLGAVLALLFLLLVLLLLVRKKRK

IKEPLLLPEDDTRDNVFYYGEEGGGEEDQDYDITQLHRGLEARPEVVLRNDVAPTIIP

TPMYRPRPANPDEIGNFIIENLKAANTDPTAPPYDTLLVFDYEGSGSDAASLSSLTSS

ASDQDQDYDYLNEWGSRFKKLADMYGGGEDD (SEQ ID NO:86)

FIGURE 46B

CONT (NM_001843)

```
   1 gctgtgccgc accgaggcga gcaggagcag ggaacaggtg tttaaaatta tccaactgcc
  61 atagagctaa attctttttt ggaaaattga accgaacttc tactgaatac aagatgaaaa
 121 tgtggttgct ggtcagtcat cttgtgataa tatctattac tacctgttta gcagagttta
 181 catggtatag aagatatggt catggagttt ctgaggaaga caaaggattt ggaccaattt
 241 ttgaagagca gccaatcaat accatttatc cagaggaatc actggaagga aaagtctcac
 301 tcaactgtag ggcacgagcc agccctttcc cggtttacaa atggagaatg aataatgggg
 361 acgttgatct cacaagtgat cgatacagta tggtaggagg aaaccttgtt atcaacaacc
 421 ctgacaaaca gaaagatgct ggaatatact actgtttagc atctaataac tacgggatgg
 481 tcagaagcac tgaagcaacc ctgagctttg gatatcttga tcctttccca cctgaggaac
 541 gtcctgaggt cagagtaaaa gaagggaaag gaatggtgct tctctgtgac cccccatacc
 601 attttccaga tgatcttagc tatcgctggc ttctaaatga atttcctgta tttatcacaa
 661 tggataaacg gcgatttgtg tctcagacaa atggcaatct ctacattgca aatgttgagg
 721 cttccgacaa aggcaattat tcctgctttg tttccagtcc ttctattaca aagagcgtgt
 781 tcagcaaatt catcccactc attccaatac ctgaacgaac aacaaaacca tatcctgctg
 841 atattgtagt tcagttcaag gatgtatatg cattgatggg ccaaaatgtg accttagaat
 901 gttttgcact tggaaatcct gttccggata tccgatggcg gaaggttcta gaaccaatgc
 961 caagcactgc tgagattagc acctctgggg ctgttcttaa gatcttcaat attcagctag
1021 aagatgaagg catctatgaa tgtgaggctg agaacattag aggaaaggat aaacatcaag
1081 caagaattta tgttcaagca ttccctgagt gggtagaaca catcaatgac acagaggtgg
1141 acataggcag tgatctctac tggccttgtg tggccacagg aaagcccatc cctacaatcc
1201 gatggttgaa aaatggatat gcgtatcata aaggggaatt aagactgtat gatgtgactt
1261 ttgaaaatgc cggaatgtat cagtgcatag ctgaaaacac atatggagcc atttatgcaa
1321 atgctgagtt gaagatcttg gcgttggctc caacttttga aatgaatcct atgaagaaaa
1381 agatcctggc tgctaaaggt ggaagggtga taattgaatg caaacctaaa gctgcaccga
1441 aaccaaagtt ttcatggagt aaagggacag agtggcttgt caatagcagc agaatactca
1501 tttgggaaga tggtagcttg gaaatcaaca acattacaag gaatgatgga ggtatctata
1561 catgctttgc agaaaataac agagggaaag ctaatagcac tggaaccctt gttatcacag
1621 atcctacgcg aattatattg gccccaatta atgccgatat cacagttgga gaaaacgcca
1681 ccatgcagtg tgctgcgtcc tttgatcctg ccttggatct cacatttgtt tggtccttca
1741 atggctatgt gatcgatttt aacaaagaga atattcacta ccagaggaat tttatgctgg
1801 attccaatgg ggaattacta atccgaaatg cgcagctgaa acatgctgga agatacacat
1861 gcactgccca gacaattgtg gacaattctt cagcttcagc tgaccttgta gtgagaggcc
1921 ctccaggccc tccaggtggt ctgagaatag aagacattag agccacttct gtggcactta
1981 cttggagccg tggttcagac aatcatagtc ctatttctaa atacactatc cagaccaaga
2041 ctattctttc agatgactgg aaagatgcaa agacagatcc cccaattatt gaaggaaata
2101 tggaggcagc aagagcagtg gacttaatcc catggatgga gtatgaattc cgcgtggtag
2161 caaccaatac actgggtaga ggagagccca gtataccatc taacagaatt aaaacagacg
2221 gtgctgcacc aaatgtggct ccttcagatg taggaggtgg aggtggaaga aacagagagc
2281 tgaccataac atgggcgcct ttgtcaagag aataccacta tggcaacaat tttggttaca
2341 tagtggcatt taagccattt gatggagaag aatggaaaaa agtcacagtt actaatcctg
2401 atactggccg atatgtccat aaagatgaaa ccatgagccc ttccactgca tttcaagtta
2461 aagtcaaggc cttcaacaac aaaggagatg gaccttacag cctagtagca gtcattaatt
2521 cagcacaaga cgctcccagt gaagccccaa cagaagtagg tgtaaaagtc ttatcatctt
2581 ctgagatatc tgttcattgg gaacatgttt tagaaaaaat agtggaaagc tatcagattc
2641 ggtattgggc tgcccatgac aaagaagaag ctgcaaacag agttcaagtc accagccaag
2701 agtactcggc caggctcgag aaccttctgc cagacaccca gtattttata gaagtcgggg
2761 cctgcaatag tgcagggtgt ggacctccaa gtgacatgat tgaggctttc accaagaaag
2821 cacctcctag ccagcctcca aggatcatca gttcagtaag gtctggttca cgctatataa
2881 tcacctggga tcatgtcgtt gcactatcaa atgaatctac agtgacggga tataaggtac
2941 tctacagacc tgatggccag catgatggca agctgtattc aactcacaaa cactccatag
3001 aagtcccaat ccccagagat ggagaatacg ttgtggaggt tcgcgcgcac agtgatggag
3061 gagatggagt ggtgtctcaa gtcaaaattt caggtgcacc caccctatcc ccaagtcttc
3121 tcggcttact gctgcctgcc tttggcatcc ttgtctactt ggaattctga atgtgttgtg
3181 acagctgctg ttcccatccc agctcagaag acacccttca accctgggat gaccacaatt
3241 ccttccaatt tctgcggctc catcctaagc caaataaatt atactttaac aaactattca
3301 actgatttac aacacacatg atgactgagg cattcgggaa ccccttcatc caaaagaata
3361 aacttttaaa tggatataaa tgatttttaa ctcgttccaa tatgccttat aaaccactta
3421 acctgat (SEQ ID NO:87)
```

FIGURE 47A

CONT (NM_001843)

MKMWLLVSHLVIISITTCLAEFTWYRRYGHGVSEEDKGFGPIFE

EQPINTIYPEESLEGKVSLNCRARASPFPVYKWRMNNGDVDLTSDRYSMVGGNLVINN

PDKQKDAGIYYCLASNNYGMVRSTEATLSFGYLDPFPPEERPEVRVKEGKGMVLLCDP

PYHFPDDLSYRWLLNEFPVFITMDKRRFVSQTNGNLYIANVEASDKGNYSCFVSSPSI

TKSVFSKFIPLIPIPERTTKPYPADIVVQFKDVYALMGQNVTLECFALGNPVPDIRWR

KVLEPMPSTAEISTSGAVLKIFNIQLEDEGIYECEAENIRGKDKHQARIYVQAFPEWV

EHINDTEVDIGSDLYWPCVATGKPIPTIRWLKNGYAYHKGELRLYDVTFENAGMYQCI

AENTYGAIYANAELKILALAPTFEMNPMKKKILAAKGGRVIIECKPKAAPKPKFSWSK

GTEWLVNSSRILIWEDGSLEINNITRNDGGIYTCFAENNRGKANSTGTLVITDPTRII

LAPINADITVGENATMQCAASFDPALDLTFVWSFNGYVIDFNKENIHYQRNFMLDSNG

ELLIRNAQLKHAGRYTCTAQTIVDNSSASADLVVRGPPGPPGGLRIEDIRATSVALTW

SRGSDNHSPISKYTIQTKTILSDDWKDAKTDPPIIEGNMEAARAVDLIPWMEYEFRVV

ATNTLGRGEPSIPSNRIKTDGAAPNVAPSDVGGGGGRNRELTITWAPLSREYHYGNNF

GYIVAFKPFDGEEWKKVTVTNPDTGRYVHKDETMSPSTAFQVKVKAFNNKGDGPYSLV

AVINSAQDAPSEAPTEVGVKVLSSSEISVHWEHVLEKIVESYQIRYWAAHDKEEAANR

VQVTSQEYSARLENLLPDTQYFIEVGACNSAGCGPPSDMIEAFTKKAPPSQPPRIISS

VRSGSRYIITWDHVVALSNESTVTGYKVLYRPDGQHDGKLYSTHKHSIEVPIPRDGEY

VVEVRAHSDGGDGVVSQVKISGAPTLSPSLLGLLLPAFGILVYLEF (SEQ ID NO:88)

FIGURE 47B

Osteopontin (NM_000582)

```
   1 ctccctgtgt tggtggagga tgtctgcagc agcatttaaa ttctgggagg gcttggttgt
  61 cagcagcagc aggaggaggc agagcacagc atcgtcggga ccagactcgt ctcaggccag
 121 ttgcagcctt ctcagccaaa cgccgaccaa ggaaaactca ctaccatgag aattgcagtg
 181 atttgctttt gcctcctagg catcacctgt gccataccag ttaaacaggc tgattctgga
 241 agttctgagg aaaagcagct ttacaacaaa tacccagatg ctgtggccac atggctaaac
 301 cctgacccat ctcagaagca gaatctccta gccccacaga cccttccaag taagtccaac
 361 gaaagccatg accacatgga tgatatggat gatgaagatg atgatgacca tgtggacagc
 421 caggactcca ttgactcgaa cgactctgat gatgtagatg acactgatga ttctcaccag
 481 tctgatgagt ctcaccattc tgatgaatct gatgaactgg tcactgattt tcccacggac
 541 ctgccagcaa ccgaagtttt cactccagtt gtccccacag tagacacata tgatggccga
 601 ggtgatagtg tggtttatgg actgaggtca aaatctaaga agtttcgcag acctgacatc
 661 cagtaccctg atgctacaga cgaggacatc acctcacaca tggaaagcga ggagttgaat
 721 ggtgcataca aggccatccc cgttgcccag gacctgaacg cgccttctga ttgggacagc
 781 cgtgggaagg acagttatga aacgagtcag ctggatgacc agagtgctga aacccacagc
 841 cacaagcagt ccagattata taagcggaaa gccaatgatg agagcaatga gcattccgat
 901 gtgattgata gtcaggaact ttccaaagtc agccgtgaat tccacagcca tgaatttcac
 961 agccatgaag atatgctggt tgtagacccc aaaagtaagg aagaagataa acacctgaaa
1021 tttcgtattt ctcatgaatt agatagtgca tcttctgagg tcaattaaaa ggagaaaaaa
1081 tacaatttct cactttgcat ttagtcaaaa gaaaaaatgc tttatagcaa aatgaaagag
1141 aacatgaaat gcttctttct cagtttattg gttgaatgtg tatctatttg agtctggaaa
1201 taactaatgt gtttgataat tagtttagtt tgtggcttca tggaaactcc ctgtaaacta
1261 aaagcttcag ggttatgtct atgttcattc tatagaagaa atgcaaacta tcactgtatt
1321 ttaatatttg ttattctctc atgaatagaa atttatgtag aagcaaacaa aatactttta
1381 cccacttaaa aagagaatat aacattttat gtcactataa tcttttgttt tttaagttag
1441 tgtatatttt gttgtgatta tctttttgtg gtgtgaataa atcttttatc ttgaatgtaa
1501 taagaatttg gtggtgtcaa ttgcttattt gttttcccac ggttgtccag caattaataa
1561 aacataacct tttttactgc ctaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa (SEQ
ID NO:89)
```

FIGURE 48A

Osteopontin (NM_000582)

MRIAVICFCLLGITCAIPVKQADSGSSEEKQLYNKYPDAVATWL

NPDPSQKQNLLAPQTLPSKSNESHDHMDDMDDEDDDDHVDSQDSIDSNDSDDVDDTDD

SHQSDESHHSDESDELVTDFPTDLPATEVFTPVVPTVDTYDGRGDSVVYGLRSKSKKF

RRPDIQYPDATDEDITSHMESEELNGAYKAIPVAQDLNAPSDWDSRGKDSYETSQLDD

QSAETHSHKQSRLYKRKANDESNEHSDVIDSQELSKVSREFHSHEFHSHEDMLVVDPK

SKEEDKHLKFRISHELDSASSEVN (SEQ ID NO:90)

FIGURE 48B

Galectin 8 (NM_006499)

```
   1 tggacttgga tccgaggcag acgaggaagc tgagaaaacc ctggcgttga ccccgtggac
  61 ctgggcgccc cgggaaggtc cagcgcttgg tccaggcagg cggggatgtg cggtgaccac
 121 cctggtcctg aaaagtccag ccccgaatct ccctccctcc tagacctgga ggcctggaac
 181 agccagccgc ccacggacgc cagagccggg aaccctgacg gcacttagct gctgacaaac
 241 aacctgctcc gtggacgcct gaaacaccag tctttggggc cagtgcctca gtttcaatcc
 301 aggtaacctt taaatgaaac ttgcctaaaa tcttaggtca tacacagaag agactccaat
 361 cgacaagaag ctggaaaaga atgatgttgt ccttaaacaa cctacagaat atcatctata
 421 acccggtaat cccgtatgtt ggcaccattc ccgatcagct ggatcctgga actttgattg
 481 tgatatgtgg gcatgttcct agtgacgcag acagattcca ggtggatctg cagaatggca
 541 gcagtgtgaa acctcgagcc gatgtggcct ttcatttcaa tcctcgtttc aaaagggccg
 601 gctgcattgt ttgcaatact ttgataaatg aaaaatgggg acgggaagag atcacctatg
 661 acacgccttt caaaagagaa aagtcttttg agatcgtgat tatggtgcta aaggacaaat
 721 tccaggtggc tgtaaatgga aaacatactc tgctctatgg ccacaggatc ggcccagaga
 781 aaatagacac tctgggcatt tatggcaaag tgaatattca ctcaattggt tttagcttca
 841 gctcggactt acaaagtacc caagcatcta gtctggaact gacagagata agtagagaaa
 901 atgttccaaa gtctggcacg ccccagcttc agactgtctc tccctcctgg gatttacagg
 961 gtcatggctc tgaaacattc tgtagtgttc tttggacacg agttttcctg gagatcgctt
1021 tctgcaggcc tattggtctg actgtggctt cttttcagag cctgccattc gctgcaaggt
1081 tgaacacccc catgggccct ggacgaactg tcgtcgttaa aggagaagtg aatgcaaatg
1141 ccaaaagctt taatgttgac ctactagcag gaaaatcaaa ggatattgct ctacacttga
1201 acccacgcct gaatattaaa gcatttgtaa gaaattcttt tcttcaggag tcctggggag
1261 aagaagagag aaatattacc tctttcccat ttagtcctgg gatgtacttt gagatgataa
1321 tttactgtga tgttagagaa ttcaaggttg cagtaaatgg cgtacacagc ctggagtaca
1381 aacacagatt taaagagctc agcagtattg acacgctgga aattaatgga gacatccact
1441 tactggaagt aaggagctgg tagcctacct acacagctgc tacaaaaacc aaaatacaga
1501 atggcttctg tgatactggc cttgctgaaa cgcatctcac tgtcattcta ttgtttatat
1561 tgttaaaatg agcttgtgca ccattagatc ctgctgggtg ttctcagtcc ttgccatgaa
1621 gtatggtggt gtctagcact gaatggggaa actgggggca gcaacactta tagccagtta
1681 aagccactct gccctctctc ctactttggc tgactcttca agaatgccat tcaacaagta
1741 tttatggagt acctactata atacagtagc taacatgtat tgagcacaga ttttttttgg
1801 taaaactgtg aggagctagg atatatactt ggtgaaacaa accagtatgt tccctgttct
1861 cttgagcttc gactcttctg tgctctattg ctgcgcactg ctttttctac aggcattaca
1921 tcaactccta aggggtcctc tgggattagt taagcagcta ttaaatcacc cgaagacact
1981 aatttacaga agacacaact ccttccccag tgatcactgt cataaccagt gctctaccgt
2041 atcccatcac tgaggactga tgttgactga catcatttta tcgtaataaa catgtggctc
2101 tattagctgc aagctttacc aagtaattgg catgacatct gagcacagaa attaaggcaa
2161 aaaaccaaag caaaacaaat acatggtgct gaaattaact tgatgccaag cccaaggcag
2221 ctgatttctg tgtatttgaa cttagggcaa atcagagtct acacagacgc ctacagaaag
2281 tttcaggaag aggcaagatg cattcaattt gaaagatatt tatgggcaac aaagtaaggt
2341 caggattaga cttcaggcat tcataaggca ggcactatca gaaagtgtac gccaactaag
2401 ggacccacaa agcaggcaga ggtaatgcag aaatctgttt tgttcccatg aaatcaccaa
2461 tcaaggcctc cgttcttcta aagattagtc catcatcatt agcaactgag atcaaagcac
2521 tcttccactt tacgtgatta aaatcaaacc tgtatcagca aaaaaaaaaa aaaaaaaaaa
2581 aaaaaaaaaa aaa (SEQ ID NO:91)
```

FIGURE 49A

Galectin 8 (NM_006499)

MLSLNNLQNIIYNPVIPYVGTIPDQLDPGTLIVICGHVPSDADR

FQVDLQNGSSVKPRADVAFHFNPRFKRAGCIVCNTLINEKWGREEITYDTPFKREKSF

EIVIMVLKDKFQVAVNGKHTLLYGHRIGPEKIDTLGIYGKVNIHSIGFSFSSDLQSTQ

ASSLELTEISRENVPKSGTPQLQTVSPSWDLQGHGSETFCSVLWTRVFLEIAFCRPIG

LTVASFQSLPFAARLNTPMGPGRTVVVKGEVNANAKSFNVDLLAGKSKDIALHLNPRL

NIKAFVRNSFLQESWGEEERNITSFPFSPGMYFEMIIYCDVREFKVAVNGVHSLEYKH

RFKELSSIDTLEINGDIHLLEVRSW (SEQ ID NO:92)

FIGURE 49B

PGS1 (bihlycan, NM_001711)

```
   1 agcctcccgc ccgccgcctc tgtctccctc tctccacaaa ctgcccagga gtgagtagct
  61 gctttcggtc cgccggacac accggacaga tagacgtgcg gacggcccac caccccagcc
 121 cgccaactag tcagcctgcg cctggcgcct cccctctcca ggtccatccg ccatgtggcc
 181 cctgtggcgc ctcgtgtctc tgctggccct gagccaggcc ctgccctttg agcagagagg
 241 cttctgggac ttcaccctgg acgatgggcc attcatgatg aacgatgagg aagcttcggg
 301 cgctgacacc tcgggcgtcc tggacccgga ctctgtcaca cccacctaca gcgccatgtg
 361 tcctttcggc tgccactgcc acctgcgggt ggttcagtgc tccgacctgg gtctgaagtc
 421 tgtgcccaaa gagatctccc ctgacaccac gctgctggac ctgcagaaca acgacatctc
 481 cgagctccgc aaggatgact tcaagggtct ccagcacctc tacgccctcg tcctggtgaa
 541 caacaagatc tccaagatcc atgagaaggc cttcagccca ctgcggaagc tgcagaagct
 601 ctacatctcc aagaaccacc tggtggagat cccgcccaac ctacccagct ccctggtgga
 661 gctccgcatc cacgacaacc gcatccgcaa ggtgcccaag ggagtgttca gcgggctccg
 721 gaacatgaac tgcatcgaga tgggcgggaa cccactggag aacagtggct ttgaacctgg
 781 agccttcgat ggcctgaagc tcaactacct gcgcatctca gaggccaagc tgactggcat
 841 ccccaaagac ctccctgaga ccctgaatga actccaccta gaccacaaca aaatccaggc
 901 catcgaactg gaggacctgc ttcgctactc caagctgtac aggctgggcc taggccacaa
 961 ccagatcagg atgatcgaga acgggagcct gagcttcctg cccaccctcc gggagctcca
1021 cttggacaac aacaagttgg ccagggtgcc ctcagggctc ccagacctca agctcctcca
1081 ggtggtctat ctgcactcca acaacatcac caaagtgggt gtcaacgact tctgtcccat
1141 gggcttcggg gtgaagcggg cctactacaa cggcatcagc ctcttcaaca accccgtgcc
1201 ctactgggag gtgcagccgg ccactttccg ctgcgtcact gaccgcctgg ccatccagtt
1261 tggcaactac aaaaagtaga ggcagctgca gccaccgcgg ggcctcagtg ggggtctctg
1321 gggaacacag ccagacatcc tgatggggag gcagagccag gaagctaagc cagggcccag
1381 ctgcgtccaa cccagccccc cacctcgggt ccctgacccc agctcgatgc cccatcaccg
1441 cctctccctg gctcccaagg gtgcaggtgg gcgcaaggcc cggcccccat cacatgttcc
1501 cttggcctca gagctgcccc tgctctccca ccacagccac ccagaggcac cccatgaagc
1561 ttttttctcg ttcactccca aacccaagtg tccaaggctc cagtcctagg agaacagtcc
1621 ctgggtcagc agccaggagg cggtccataa gaatggggac agtgggctct gccagggctg
1681 ccgcacctgt ccagacacac atgttctgtt cctcctcctc atgcatttcc agcctttcaa
1741 ccctccccga ctctgcggct cccctcagcc cccttgcaag ttcatggcct gtccctccca
1801 gacccctgct ccactggccc ttcgaccagt cctcccttct gttctctctt tccccgtcct
1861 tcctctctct ctctctctct ctctctctct ctttctgtgt gtgtgtgtgt gtgtgtgtgt
1921 gtgtgtgtgt gtgtgtgtgt cttgtgcttc ctcagacctt tctcgcttct gagcttggtg
1981 gcctgttccc tccatctctc cgaacctggc ttcgcctgtc cctttcactc cacaccctct
2041 ggccttctgc cttgagctgg gactgctttc tgtctgtccg gcctgcaccc agcccctgcc
2101 cacaaaaccc cagggacagc ggtctcccca gcctgccctg ctcaggcctt gccccaaac
2161 ctgtactgtc ccggaggagg ttgggaggtg gaggcccagc atcccgcgca gatgacacca
2221 tcaaccgcca gagtcccaga caccggtttt cctagaagcc cctcacccc actggcccac
2281 tggtggctag gtctcccctt atccttctgg tccagcgcaa ggaggggctg cttctgaggt
2341 cggtggctgt ctttccatta aagaaacacc gtgcaacgtg aaaaaaaaaa aaaaaaaaaa
2401 a (SEQ ID NO:93)
```

FIGURE 50A

PGS1 (bihlycan, NM_001711)

MWPLWRLVSLLALSQALPFEQRGFWDFTLDDGPFMMNDEEASGA

DTSGVLDPDSVTPTYSAMCPFGCHCHLRVVQCSDLGLKSVPKEISPDTTLLDLQNNDI

SELRKDDFKGLQHLYALVLVNNKISKIHEKAFSPLRKLQKLYISKNHLVEIPPNLPSS

LVELRIHDNRIRKVPKGVFSGLRNMNCIEMGGNPLENSGFEPGAFDGLKLNYLRISEA

KLTGIPKDLPETLNELHLDHNKIQAIELEDLLRYSKLYRLGLGHNQIRMIENGSLSFL

PTLRELHLDNNKLARVPSGLPDLKLLQVVYLHSNNITKVGVNDFCPMGFGVKRAYYNG

ISLFNNPVPYWEVQPATFRCVTDRLAIQFGNYKK (SEQ ID NO:94)

FIGURE 50B

Frizzled 2 (NM_001466)

```
   1 cgagtaaagt ttgcaaagag gcgcgggagg cggcagccgc agcgaggagg cggcggggaa
  61 gaagcgcagt ctccgggttg ggggcggggg cgggggggcc gccaaggagc cgggtggggg
 121 gcggcggcca gcatgcggcc ccgcagcgcc ctgccccgcc tgctgctgcc gctgctgctg
 181 ctgcccgccg ccgggccggc ccagttccac ggggagaagg gcatctccat cccggaccac
 241 ggcttctgcc agcccatctc catcccgctg tgcacggaca tcgcctacaa ccagaccatc
 301 atgcccaacc ttctgggcca cacgaaccag gaggacgcag gcctagaggt gcaccagttc
 361 tatccgctgg tgaaggtgca gtgctcgccc gaactgcgct tcttcctgtg ctccatgtac
 421 gcacccgtgt gcaccgtgct ggaacaggcc atcccgccgt gccgctctat ctgtgagcgc
 481 gcgcgccagg gctgcgaagc cctcatgaac aagttcggtt ttcagtggcc cgagcgcctg
 541 cgctgcgagc acttcccgcg ccacggcgcc gagcagatct gcgtcggcca gaaccactcc
 601 gaggacggag ctcccgcgct actcaccacc gcgccgccgc cgggactgca gccgggtgcc
 661 gggggcaccc cgggtggccc gggcggcggc ggcgctcccc cgcgctacgc cacgctggag
 721 caccccttcc actgcccgcg cgtcctcaag gtgccatcct atctcagcta caagtttctg
 781 ggcgagcgtg attgtgctgc gccctgcgaa cctgcgcggc ccgatggttc catgttcttc
 841 tcacaggagg agacgcgttt cgcgcgcctc tggatcctca cctggtcggt gctgtgctgc
 901 gcttccacct tcttcactgt caccacgtac ttggtagaca tgcagcgctt ccgctaccca
 961 gagcggccta tcatttttct gtcgggctgc tacaccatgg tgtcggtggc ctacatcgcg
1021 ggcttcgtgc tccaggagcg cgtggtgtgc aacgagcgct tctccgagga cggttaccgc
1081 acggtggtgc agggcaccaa gaaggagggc tgcaccatcc tcttcatgat gctctacttc
1141 ttcagcatgg ccagctccat ctggtgggtc atcctgtcgc tcacctggtt cctggcagcc
1201 ggcatgaagt ggggccacga ggccatcgag gccaactctc agtacttcca cctggccgcc
1261 tgggccgtgc cggccgtcaa gaccatcacc atcctggcca tgggccagat cgacggcgac
1321 ctgctgagcg gcgtgtgctt cgtaggcctc aacagcctgg acccgctgcg gggcttcgtg
1381 ctagcgccgc tcttcgtgta cctgttcatc ggcacgtcct tcctcctggc cggcttcgtg
1441 tcgctcttcc gcatccgcac catcatgaag cacgacggca ccaagaccga aaagctggag
1501 cggctcatgg tgcgcatcgg cgtcttctcc gtgctctaca cagtgcccgc caccatcgtc
1561 atcgcttgct acttctacga gcaggccttc cgcgagcact gggagcgctc gtgggtgagc
1621 cagcactgca agagcctggc catcccgtgc ccggcgcact acacgccgcg catgtcgccc
1681 gacttcacgg tctacatgat caaatacctc atgacgctca tcgtgggcat cacgtcgggc
1741 ttctggatct ggtcgggcaa gacgctgcac tcgtggagga agttctacac tcgcctcacc
1801 aacagccgac acggtgagac caccgtgtga gggacgcccc caggccggaa ccgcgcggcg
1861 ctttcctccg cccggggtgg ggcccctaca gactccgtat tttatttttt taaataaaaa
1921 acgatcgaaa ccatttcact tttaggttgc tttttaaaag agaactctct gcccaacacc
1981 ccc (SEQ ID NO:95)
```

FIGURE 51A

Frizzled 2 (NM_001466)

MRPRSALPRLLLPLLLLPAAGPAQFHGEKGISIPDHGFCQPISI

PLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCTV

LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHGAEQICVGQNHSEDGA

PALLTTAPPPGLQPGAGGTPGGPGGGGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGE

RDCAAPCEPARPDGSMFFSQEETRFARLWILTWSVLCCASTFFTVTTYLVDMQRFRYP

ERPIIFLSGCYTMVSVAYIAGFVLQERVVCNERFSEDGYRTVVQGTKKEGCTILFMML

YFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKTITILAMGQ

IDGDLLSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGT

KTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSLAIPCPA

HYTPRMSPDFTVYMIKYLMTLIVGITSGFWIWSGKTLHSWRKFYTRLTNSRHGETTV (SEQ ID NO:96)

FIGURE 51B

ISLR (NM_005545)

```
   1 aagcagttgt tttgctggaa ggagggagtg cgcgggctgc cccgggctcc tccctgccgc
  61 ctcctctcag tggatggttc caggcaccct gtctggggca gggagggcac aggcctgcac
 121 atcgaaggtg gggtgggacc aggctgcccc tcgccccagc atccaagtcc tcccttgggc
 181 gcccgtggcc ctgcagactc tcagggctaa ggtcctctgt tgctttttgg ttccacctta
 241 gaagaggctc cgcttgacta agagtagctt gaaggaggca ccatgcagga gctgcatctg
 301 ctctggtggg cgcttctcct gggcctggct caggcctgcc ctgagccctg cgactgtggg
 361 gaaaagtatg gcttccagat cgccgactgt gcctaccgcg acctagaatc cgtgccgcct
 421 ggcttcccgg ccaatgtgac tacactgagc ctgtcagcca accggctgcc aggcttgccg
 481 gagggtgcct tcagggaggt gcccctgctg cagtcgctgt ggctggcaca caatgagatc
 541 cgcacggtgg ccgccggagc cctggcctct ctgagccatc tcaagagcct ggacctcagc
 601 cacaatctca tctctgactt tgcctggagc gacctgcaca acctcagtgc cctccaattg
 661 ctcaagatgg acagcaacga gctgaccttc atcccccgcg acgccttccg cagcctccgt
 721 gctctgcgct cgctgcaact caaccacaac cgcttgcaca cattggccga gggcaccttc
 781 accccgctca ccgcgctgtc ccacctgcag atcaacgaga acccccttcga ctgcacctgc
 841 ggcatcgtgt ggctcaagac atgggccctg accacggccg tgtccatccc ggagcaggac
 901 aacatcgcct gcacctcacc ccatgtgctc aagggtacgc cgctgagccg cctgccgcca
 961 ctgccatgct cggcgccctc agtgcagctc agctaccaac ccagccagga tggtgccgag
1021 ctgcggcctg gttttgtgct ggcactgcac tgtgatgtgg acgggcagcc ggcccctcag
1081 cttcactggc acatccagat acccagtggc attgtggaga tcaccagccc caacgtgggc
1141 actgatgggc gtgccctgcc tggcaccctt gtggccagct cccagccgcg cttccaggcc
1201 tttgccaatg gcagcctgct tatccccgac tttggcaagc tggaggaagg cacctacagc
1261 tgcctggcca ccaatgagct gggcagtgct gagagctcag tggacgtggc actggccacg
1321 cccggtgagg gtggtgagga cacactgggg cgcaggttcc atggcaaagc ggttgaggga
1381 aagggctgct atacggttga caacgaggtg cagccatcag ggccggagga caatgtggtc
1441 atcatctacc tcagccgtgc tgggaaccct gaggctgcag tcgcagaagg ggtccctggg
1501 cagctgcccc caggcctgct cctgctgggc caaagcctcc tcctcttctt cttcctcacc
1561 tccttctagc cccacccagg gcttccctaa ctcctccctt tgcccctacc aatgccccctt
1621 taagtgctgc aggggtctgg ggttggcaac tcctgaggcc tgcatgggtg acttcacatt
1681 ttcctacctc tccttctaat ctcttctaga gcacctgcta tccccaactt ctagacctgc
1741 tccaaactag tgactaggat agaatttgat cccctaactc actgtctgcg gtgctcattg
1801 ctgctaacag cattgcctgt gctctcctct caggggcagc atgctaacgg ggcgacgtcc
1861 taatccaact gggagaagcc tcagtggtgg aattccaggc actgtgactg tcaagctggc
1921 aagggccagg attgggggaa tggagctggg gcttagctgg gaggtggtct gaagcagaca
1981 gggaatggga gaggaggatg ggaagtagac agtggctggt atggctctga ggctccctgg
2041 ggcctgctca agctcctcct gctccttgct gttttctgat gatttggggg cttgggagtc
2101 cctttgtcct catctgagac tgaaatgtgg ggatccagga tggcttcctt cctcttaccc
2161 ttcctccctc agcctgcaac ctctatcctg gaacctgtcc tccctttctc cccaactatg
2221 catctgttgt ctgctcctct gcaaaggcca gccagcttgg gagcagcaga gaaataaaca
2281 gcatttctga tgcc (SEQ ID NO:97)
```

FIGURE 52A

ISLR (NM_005545)

MQELHLLWWALLLGLAQACPEPCDCGEKYGFQIADCAYRDLESV

PPGFPANVTTLSLSANRLPGLPEGAFREVPLLQSLWLAHNEIRTVAAGALASLSHLKS

LDLSHNLISDFAWSDLHNLSALQLLKMDSNELTFIPRDAFRSLRALRSLQLNHNRLHT

LAEGTFTPLTALSHLQINENPFDCTCGIVWLKTWALTTAVSIPEQDNIACTSPHVLKG

TPLSRLPPLPCSAPSVQLSYQPSQDGAELRPGFVLALHCDVDGQPAPQLHWHIQIPSG

IVEITSPNVGTDGRALPGTPVASSQPRFQAFANGSLLIPDFGKLEEGTYSCLATNELG

SAESSVDVALATPGEGGEDTLGRRFHGKAVEGKGCYTVDNEVQPSGPEDNVVIIYLSR

AGNPEAAVAEGVPGQLPPGLLLLGQSLLLFFFLTSF (SEQ ID NO:98)

FIGURE 52B

FLJ23399 (NM_022763)

```
   1 tgacccggtc cgtgtgggcc agcgggaagg aagccagttg agggaagttc tccatgaatg
  61 tacgtcacaa tgatgatgac cgaccaaatc cctctggaac tgccaccatt gctgaacgga
 121 gaggtagcca tgatgcccca cttggtgaat ggagatgcag ctcagcaggt tattctcgtt
 181 caagttaatc caggtgagac tttcacaata agagcagagg atggaacact tcagtgcatt
 241 caaggacctg ctgaagttcc catgatgtca cccaatggat ccattcctcc cattcatgtg
 301 cctccaggtt atatctcaca ggtgattgaa gatagtactg gagtccgccg ggtggtggtc
 361 acaccccagt ctcctgagtg ttatccccca agctacccct cagccatgtc tccaacccat
 421 catctccctc cctatctgac tcaccatcca cattttattc ataactcaca cacggcttac
 481 tacccacctg ttaccggacc tggagatatg ccgcctcagt tttttcccca gcatcatctt
 541 ccccacacaa tatatggtga gcaagaaatt ataccatttt atggaatgtc aagctacatc
 601 acccgagaag accagtacag caagcctccg cacaaaaaac tgaaagaccg ccagatcgat
 661 cgccagaacc gactcaacag acctccttct gctatctaca aaagcagctg cacaacagta
 721 tacaatggct atgggaaggg ccatagtggt ggaagtggcg gaggcggcag cggtagtggt
 781 cccggaatta agaaaacaga gcgacgagca agaagcagcc caaagtcgaa tgattcagac
 841 ttgcaagaat atgagttgga agtaaagagg gtgcaagaca ttctttcggg aatagagaaa
 901 ccacaggttt ctaatattca ggcaagagca gttgtgttgt cctgggctcc ccctgttgga
 961 ctttcctgtg gaccccacag tggtctttcc ttcccctaca gttacgaggt ggccttatca
1021 gacaaaggac gagatggaaa atacaagata atttacagtg gagaagaatt agaatgtaac
1081 ctgaaagatc ttagaccagc aacagattat catgtgaggg tgtatgccat gtacaattcc
1141 gtaaagggat cctgctccga gcctgttagc ttcaccaccc acagctgtgc acccgagtgt
1201 cctttccccc ctaagctggc acataggagc aaaagttcac taaccctgca gtggaaggca
1261 ccaattgaca acggttcaaa aatcaccaac tacctttag agtgggatga gggaaaaaga
1321 aatagtggtt tcagacagtg cttcttcggg agccagaagc actgcaagtt gacaaagctt
1381 tgtccggcaa tggggtacac attcaggctg gccgctcgaa acgacattgg taccagtggt
1441 tatagccaag aggtggtgtg ctacacatta ggaaatatcc ctcagatgcc ttctgcacca
1501 aggctggttc gagctggcat cacatgggtc acgttgcagt ggagtaagcc agaaggctgt
1561 tcacccgagg aagtgatcac ctacaccttg gaaattcagg aggatgaaaa tgataacctt
1621 ttccacccaa aatacactgg agaggattta acctgtactg tgaaaaatct caaaagaagc
1681 acacagtata cattcaggct gactgcttct aatacggaag gaaaaagctg tccaagcgaa
1741 gttcttgttt gtacgacgag tcctgacagg cctggacctc ctaccagacc gcttgtcaaa
1801 ggcccagtta catctcatgg ctttagtgtc aaatgggatc cccctaagga caatggtggt
1861 tcagaaatcc tcaagtactt gctagagatt actgatggaa attctgaagc gaatcagtgg
1921 gaagtggcct acagtgggtc ggctaccgaa tacaccttca cccacttgaa accaggcact
1981 ttgtacaaac tccgagcatg ctgcatcagt accggcggac acagccagtg ttctgaaagt
2041 ctccctgttc gcacactaag cattgcacca ggtcaatgtc gaccaccgag ggttttgggt
2101 agaccaaagc acaaagaagt ccacttagag tgggatgttc ctgcatcgga aagtggctgt
2161 gaggtctcag agtacagcgt ggagatgacg gagcccgaag acgtagcctc ggaagtgtac
2221 catggcccag agctggagtg caccgtcggc aacctgcttc ctggaaccgt gtatcgcttc
2281 cgggtgaggg ctctgaatga tggagggtat ggtccctatt ctgatgtctc agaaattacc
2341 actgctgcag ggcctcctgg acaatgcaaa gcaccttgta tttcttgtac acctgatgga
2401 tgtgtcttag tgggttggga gagtcctgat agttctggtg ctgacatctc agagtacagg
2461 ttggaatggg gagaagatga agaatcctta gaactcattt atcatgggac agacacccgt
2521 tttgaaataa gagacctgtt gcctgctgca cagtattgct gtagactaca ggccttcaat
2581 caagcagggg cagggccgta cagtgaactt gtcctttgcc agacgccagc gtctgccctt
2641 gaccccgtct ccactctctg tgtcctggag gaggagcccc ttgatgccta ccctgattca
2701 ccttctgcgt gccttgtact gaactgggaa gagccgtgca ataacggatc tgaaatcctt
2761 gcttacacca ttgatctagg agacactagc attaccgtgg gcaacaccac catgcatgtt
2821 atgaaagatc tccttccaga aaccacctac cggatcagaa ttcaggctat aaatgaaatt
2881 ggagctggac catttagtca gttcattaaa gcaaaaactc ggccattacc accttgcct
2941 cctaggctag aatgtgctgc tgctggtcct cagagcctga agctaaaatg gggagacagt
3001 aactccaaga cacatgctgc tgaggacatt gtgtacacac tacagctgga ggacagaaac
3061 aagaggttta tttcaatcta cagaggaccc agccacacct acaaggtcca gagactgacg
3121 gaattcacat gctactcctt cagaatccag gcagcaagcg aggctggaga agggccttc
3181 tcagaaacct ataccttcag cacaaccaaa agtgtccccc ccaccatcaa agcacctcga
3241 gtaacacagt tagaaggaaa ttcatgtgaa attttatggg agacggtacc atcaatgaaa
3301 ggtgaccctg ttaactacat tctgcaggta ttggttggaa gagaatctga gtacaaacag
```

FIGURE 53A

3361 gtgtacaagg gagaagaagc cacattccaa atctcaggcc tccagaccaa cacagactac
3421 aggttccgcg tatgtgcgtg tcgtcgctgt ttagacacct ctcaggagct aagcggagcc
3481 ttcagcccct ctgcggcttt tgtattacaa cgaagtgagg tcatgcttac aggggacatg
3541 gggagcttag atgatcccaa aatgaagagc atgatgccta ctgatgaaca gtttgcagcc
3601 atcattgtgc ttggctttgc aactttgtcc attttatttg cctttatatt acagtacttc
3661 ttaatgaagt aaacccaaca aaactagagg tatgaattaa tgctacacat tttaatacac
3721 acatttattc agatactccc ctttttaaag ccctttttgtt ttttgattta tatactctgt
3781 tttacagatt tagctagaaa aaaaatgtca gtgttttggt gcacctttt gaaatgcaaa
3841 actaggaaaa ggttaaactg gatttttttt tttaaaaaaa agaaaaaaaa agaagaaaag
3901 tataccagat accaaaagct agctttctta tgttttcctt taaattttca gatttacctt
3961 cattctgttt tcactgatgt cttttgcaag cctttgattt ttttttttt gttacagttt
4021 agtaatttat attcaccagt cacttcatat gtcttgaaca tctgtatctg taaacatgaa
4081 tcaccgtgtg tgtacttaca gggctaggat ttcagtgttg tcagagtatt accacacagc
4141 aacagcaaca tacagaagat atgttcactc agataagact gccctaaaca accattttgt
4201 cactcagtta tttaactgtg tttagctcat ttaaatcaaa atgtgtactt taatctaaaa
4261 tgttttaata atctgtattt cttataattt taacactatg agctgcctgt ataagaaatc
4321 aagtaaccag aatgcaccta taaattatgg agcattgtag attttaccac atcaattcat
4381 agcagtaact ttaagagggc attgtgcaat agttagttgt tttcttgttc agctatttta
4441 aaggctgctt taacttgttt gtttgtcttt gtatataact acttctaatc taatcactag
4501 agttattata ttctgttatg tttgaccaga attatatgac aagaactggt gacagtttag
4561 tgcctctgcc cattgtccat gatttacact aattgtgagc agtcttctta tgtgtcagct
4621 cattattttt gaaacatttg cctttaggct gttctttgag gtatcaatga agtgattgaa
4681 tttcaatacc ttaattcagt gcacataata ctaatgtaac agcagatgaa aattgataaa
4741 acccaaaaga gagtcatcta aatttgtagt tcctatttct gtgggtttgc ctggccatgg
4801 ttggagaggg aatggtgttt gatggtaaac acagggtgtt tggggatcaa ggagcctaga
4861 ttctctccct ggatctgtca ctaacttgct gcgtgacctg aacacgtcac tttacctctc
4921 tgtgcctcag ttttcccatg catgaaaaat aaaataaaat aaaacgggga ttctaatgtt
4981 tgtaagtgct ttgagatctt tgaccaacag gtgctattgg agtgcaaagt gttactctta
5041 cgtgtttatt ttgagtcatg agataatcaa ttttaaccca aagtcattgg attatttata
5101 tgaagtccat aatgttcgag tacctcaggg acatttaaga gttggaggtg caaatatatt
5161 ccaaaagggt gcaacagaca cagtgtatcc ccctgcttct gtttttgtat atttttgcta
5221 cttggttttt cttgatcata gctattttgt gcttgatctt tattgtctaa gatgcagtat
5281 cctgtactag cttataatat tcccatacca aagtcatggg gaaacaaaca ttattttgtt
5341 tttggtttat ttatactata ttctgcatac agtactttaa atgccaatta cagtgcaatc
5401 tttatttatt gtaaaatttt ttaagtgtac ttatgtacta attttccctt gtagcatgtt
5461 atatttttgt gttttatact tttgtaattt taggtcagtc ttgttccttg gcaacatctg
5521 tagtattatt aatcttctga cattttctta tgtttttaaa aagataagag catctagtgc
5581 attaaatgcc aaaaaaaaaa tacattatca gtgattgaaa cgtttacatg tacccaaaaa
5641 ccataatcat ctcttggaag aaaatgctga gatcaatgaa ttattctgtg tgcctatatt
5701 gacgtagtga gtactagaga gttctgtatt ttattattga ctataataat tagtttaatt
5761 agctttgcaa actgatggca tcaaggtaaa tatatttttg ccaaagttct ggccttccaa
5821 aactcacccc cttatttaaa tgtgtgctat gacccactat gaccacagca tctgcatttt
5881 ctaaaaaatt ccatgcaggt gttttgggga gaggtatttt ttaagcaatg aaaattcaac
5941 tgagtacaaa gccccctctt gggggggttgg ggaagtctct tttttgaaac acttcagaac
6001 tgctgctata aagaaattct ctaattggtt gaatttttttt tttaagtaaa tagtacttta
6061 ggccaaaatt tatatgaata tttgatcttc ttgagatttt catactatca tttaaccacc
6121 aggaagctga agtgtgtgaa gtacaaagct gacagcactt tattttattg ctctccatta
6181 tttggtattc attatattcc ttcagtcaga aaattattac tctctatggc actgtttttt
6241 atcacaaata tgtatatgtg atattgatat ataactatat atattgccat cacacacgaa
6301 caataaaata aagtgttcta ttaacctgat ctctttgccc ttttgctatg tgaggagtga
6361 atgagtggcc ttctgatgct ctgactcttc tctgtatgtc aaactcatcc ctggcacaag
6421 aaattccagt catgtgaagc aaactgccct ttgtcctcaa agaaattgtt gaaaaagaaa
6481 acttttaaa gagatttttt gcatattctc tgccttgttc ttatcaactt gaaatgttgg
6541 cattttctaa ccttgttttg ttggctacaa taattcagta ttcatgtcaa aattgagaag
6601 tgccctaatt gaatgtgttt gaatgttatc cttgcacaat tctttaaatt gaaagataaa
6661 atgttttacc tcactgttgg acatacattc caagcttttc aactctagga gaaaaagaaa
6721 atcatgtttt cctgtattgt aaatttttaga ctatttcata tacattgtat taaaactgcc
6781 atatcaattt taatgtatag attttgcaaa tattatgcta tatgtaatac ctaactgtat
6841 ctgtagtgta tatgtaatat atttatgccc aataaatgtt ttaattcttt ctga (SEQ ID NO:99)

FIGURE 53B

FLJ23399 (NM_022763)

MYVTMMMTDQIPLELPPLLNGEVAMMPHLVNGDAAQQVILVQVN

PGETFTIRAEDGTLQCIQGPAEVPMMSPNGSIPPIHVPPGYISQVIEDSTGVRRVVVT

PQSPECYPPSYPSAMSPTHHLPPYLTHHPHFIHNSHTAYYPPVTGPGDMPPQFFPQHH

LPHTIYGEQEIIPFYGMSSYITREDQYSKPPHKKLKDRQIDRQNRLNRPPSAIYKSSC

TTVYNGYGKGHSGGSGGGGSGSGPGIKKTERRARSSPKSNDSDLQEYELEVKRVQDIL

SGIEKPQVSNIQARAVVLSWAPPVGLSCGPHSGLSFPYSYEVALSDKGRDGKYKIIYS

GEELECNLKDLRPATDYHVRVYAMYNSVKGSCSEPVSFTTHSCAPECPFPPKLAHRSK

SSLTLQWKAPIDNGSKITNYLLEWDEGKRNSGFRQCFFGSQKHCKLTKLCPAMGYTFR

LAARNDIGTSGYSQEVVCYTLGNIPQMPSAPRLVRAGITWVTLQWSKPEGCSPEEVIT

YTLEIQEDENDNLFHPKYTGEDLTCTVKNLKRSTQYTFRLTASNTEGKSCPSEVLVCT

TSPDRPGPPTRPLVKGPVTSHGFSVKWDPPKDNGGSEILKYLLEITDGNSEANQWEVA

YSGSATEYTFTHLKPGTLYKLRACCISTGGHSQCSESLPVRTLSIAPGQCRPPRVLGR

PKHKEVHLEWDVPASESGCEVSEYSVEMTEPEDVASEVYHGPELECTVGNLLPGTVYR

FRVRALNDGGYGPYSDVSEITTAAGPPGQCKAPCISCTPDGCVLVGWESPDSSGADIS

EYRLEWGEDEESLELIYHGTDTRFEIRDLLPAAQYCCRLQAFNQAGAGPYSELVLCQT

PASAPDPVSTLCVLEEEPLDAYPDSPSACLVLNWEEPCNNGSEILAYTIDLGDTSITV

GNTTMHVMKDLLPETTYRIRIQAINEIGAGPFSQFIKAKTRPLPPLPPRLECAAAGPQ

SLKLKWGDSNSKTHAAEDIVYTLQLEDRNKRFISIYRGPSHTYKVQRLTEFTCYSFRI

QAASEAGEGPFSETYTFSTTKSVPPTIKAPRVTQLEGNSCEILWETVPSMKGDPVNYI

LQVLVGRESEYKQVYKGEEATFQISGLQTNTDYRFRVCACRRCLDTSQELSGAFSPSA

AFVLQRSEVMLTGDMGSLDDPKMKSMMPTDEQFAAIIVLGFATLSILFAFILQYFLMK (SEQ ID NO:100)

FIGURE 53C

TEM1 (NM_020404)

```
   1 tcgcgatgct gctgcgcctg ttgctggcct gggcggccgc agggcccaca ctgggccagg
  61 acccctgggc tgctgagccc cgtgccgcct gcggccccag cagctgctac gctctcttcc
 121 cacggcgccg caccttcctg gaggcctggc gggcctgccg cgagctgggg ggcgacctgg
 181 ccactcctcg gaccccgag gaggcccagc gtgtggacag cctggtgggt gcgggcccag
 241 ccagccggct gctgtggatc gggctgcagc ggcaggcccg gcaatgccag ctgcagcgcc
 301 cactgcgcgg cttcacgtgg accacagggg accaggacac ggctttcacc aactgggccc
 361 agccagcctc tggaggcccc tgcccggccc agcgctgtgt ggccctggag gcaagtggcg
 421 agcaccgctg gctggagggc tcgtgcacgc tggctgtcga cggctacctg tgccagtttg
 481 gcttcgaggg cgcctgcccg gcgctgcaag atgaggcggg ccaggccggc ccagccgtgt
 541 ataccacgcc cttccacctg gtctccacag agtttgagtg gctgcccttc ggctctgtgg
 601 ccgctgtgca gtgccaggct ggcaggggag cctctctgct ctgcgtgaag cagcctgagg
 661 gaggtgtggg ctggtcacgg gctgggcccc tgtgcctggg gactggctgc agccctgaca
 721 acgggggctg cgaacacgaa tgtgtggagg aggtggatgg tcacgtgtcc tgccgctgca
 781 ctgagggctt ccggctggca gcagacgggc gcagttgcga ggacccctgt gcccaggctc
 841 cgtgcgagca gcagtgtgag cccggtgggc cacaaggcta cagctgccac tgtcgcctgg
 901 gtttccggcc agcggaggat gatccgcacc gctgtgtgga cacagatgag tgccagattg
 961 ccggtgtgtg ccagcagatg tgtgtcaact acgttggtgg cttcgagtgt tattgtagcg
1021 agggacatga gctggaggct gatggcatca gctgcagccc tgcagggcc atgggtgccc
1081 aggcttccca ggacctcgga gatgagttgc tggatgacgg ggaggatgag gaagatgaag
1141 acgaggcctg gaaggccttc aacggtggct ggacggagat gcctgggatc ctgtggatgg
1201 agcctacgca gccgcctgac tttgccctgg cctatagacc gagcttccca gaggacagag
1261 agccacagat accctacccg gagcccacct ggccaccccc gctcagtgcc cccagggtcc
1321 cctaccactc ctcagtgctc tccgtcaccc ggcctgtggt ggtctctgcc acgcatccca
1381 cactgccttc tgcccaccag cctcctgtga tccctgccac acacccagct ttgtcccgtg
1441 accaccagat ccccgtgatc gcagccaact atccagatct gccttctgcc taccaacccg
1501 gtattctctc tgtctctcat tcagcacagc ctcctgccca ccagcccctt atgatctcaa
1561 ccaaatatcc ggagctcttc cctgcccacc agtcccccat gtttccagac acccgggtcg
1621 ctggcaccca gaccaccact catttgcctg gaatcccacc taaccatgcc cctctggtca
1681 ccaccctcgg tgcccagcta ccccctcaag ccccagatgc ccttgtcctc agaacccagg
1741 ccacccagct tcccattatc ccaactgccc agccctctct gaccaccacc tccaggtccc
1801 ctgtgtctcc tgcccatcaa atctctgtgc ctgctgccac ccagcccgca gccctcccca
1861 ccctcctgcc ctctcagagc cccactaacc agacctcacc catcagccct acacatcccc
1921 attccaaagc cccccaaatc ccaagggaag atggccccag tcccaagttg gccctgtggc
1981 tgccctcacc agctcccaca gcagccccaa cagccctggg ggaggctggt cttgccgagc
2041 acagccagag ggatgaccgg tggctgctgg tggcactcct ggtgccaacg tgtgtctttt
2101 tggtggtcct gcttgcactg ggcatcgtgt actgcacccg ctgtggcccc catgcaccca
2161 acaagcgcat cactgactgc tatcgctggg tcatccatgc tgggagcaag agcccaacag
2221 aacccatgcc ccccaggggc agcctcacag gggtgcagac ctgcagaacc agcgtgtgat
2281 ggggtgcaga ccccctcat ggagtatggg gcgctggaca catggccggg gctgcaccag
2341 ggacccatgg gggctgccca gctggacaga tggcttcctg ctccccaggc ccagccaggg
2401 tcctctctca accactagac ttggctctca ggaactctgc ttcctggccc agcgctcgtg
2461 accaaggata caccaaagcc cttaagacct caggggcgg gtgctggggt cttctccaat
2521 aaatggggtg tcaaccttaa aaaaaaaaaa aaaaaaaaaa aaaaa (SEQ ID NO:101)
```

FIGURE 54A

TEM1 (NM_020404)

MLLRLLLAWAAAGPTLGQDPWAAEPRAACGPSSCYALFPRRRTF

LEAWRACRELGGDLATPRTPEEAQRVDSLVGAGPASRLLWIGLQRQARQCQLQRPLRG

FTWTTGDQDTAFTNWAQPASGGPCPAQRCVALEASGEHRWLEGSCTLAVDGYLCQFGF

EGACPALQDEAGQAGPAVYTTPFHLVSTEFEWLPFGSVAAVQCQAGRGASLLCVKQPE

GGVGWSRAGPLCLGTGCSPDNGGCEHECVEEVDGHVSCRCTEGFRLAADGRSCEDPCA

QAPCEQQCEPGGPQGYSCHCRLGFRPAEDDPHRCVDTDECQIAGVCQQMCVNYVGGFE

CYCSEGHELEADGISCSPAGAMGAQASQDLGDELLDDGEDEEDEDEAWKAFNGGWTEM

PGILWMEPTQPPDFALAYRPSFPEDREPQIPYPEPTWPPPLSAPRVPYHSSVLSVTRP

VVVSATHPTLPSAHQPPVIPATHPALSRDHQIPVIAANYPDLPSAYQPGILSVSHSAQ

PPAHQPPMISTKYPELFPAHQSPMFPDTRVAGTQTTTHLPGIPPNHAPLVTTLGAQLP

PQAPDALVLRTQATQLPIIPTAQPSLTTTSRSPVSPAHQISVPAATQPAALPTLLPSQ

SPTNQTSPISPTHPHSKAPQIPREDGPSPKLALWLPSPAPTAAPTALGEAGLAEHSQR

DDRWLLVALLVPTCVFLVVLLALGIVYCTRCGPHAPNKRITDCYRWVIHAGSKSPTEP

MPPRGSLTGVQTCRTSV (SEQ ID NO:102)

FIGURE 54B

Tie2 ligand2 (NM_001147)

```
   1 tgggttggtg tttatctcct cccagccttg agggagggaa caacactgta ggatctgggg
  61 agagaggaac aaaggaccgt gaaagctgct ctgtaaaagc tgacacagcc ctcccaagtg
 121 agcaggactg ttcttcccac tgcaatctga cagtttactg catgcctgga gagaacacag
 181 cagtaaaaac caggtttgct actggaaaaa gaggaaagag aagactttca ttgacggacc
 241 cagccatggc agcgtagcag ccctgcgttt cagacggcag cagctcggga ctctggacgt
 301 gtgtttgccc tcaagtttgc taagctgctg gtttattact gaagaaagaa tgtggcagat
 361 tgttttcttt actctgagct gtgatcttgt cttggccgca gcctataaca actttcggaa
 421 gagcatggac agcataggaa agaagcaata tcaggtccag catgggtcct gcagctacac
 481 tttcctcctg ccagagatgg acaactgccg ctcttcctcc agcccctacg tgtccaatgc
 541 tgtgcagagg gacgcgccgc tcgaatacga tgactcggtg cagaggctgc aagtgctgga
 601 gaacatcatg gaaaacaaca ctcagtggct aatgaagctt gagaattata tccaggacaa
 661 catgaagaaa gaaatggtag agatacagca gaatgcagta cagaaccaga cggctgtgat
 721 gatagaaata gggacaaacc tgttgaacca aacagctgag caaacgcgga agttaactga
 781 tgtggaagcc caagtattaa atcagaccac gagacttgaa cttcagctct tggaacactc
 841 cctctcgaca aacaaattgg aaaaacagat tttggaccag accagtgaaa taaacaaatt
 901 gcaagataag aacagtttcc tagaaaagaa ggtgctagct atggaagaca agcacatcat
 961 ccaactacag tcaataaaag aagagaaaga tcagctacag gtgttagtat ccaagcaaaa
1021 ttccatcatt gaagaactag aaaaaaaaat agtgactgcc acggtgaata attcagttct
1081 tcaaaagcag caacatgatc tcatggagac agttaataac ttactgacta tgatgtccac
1141 atcaaactca gctaaggacc ccactgttgc taaagaagaa caaatcagct tcagagactg
1201 tgctgaagta ttcaaatcag gacacaccac aaatggcatc tacacgttaa cattccctaa
1261 ttctacagaa gagatcaagg cctactgtga catggaagct ggaggaggcg ggtggacaat
1321 tattcagcga cgtgaggatg gcagcgttga ttttcagagg acttggaaag aatataaagt
1381 gggatttggt aacccttcag gagaatattg gctgggaaat gagtttgttt cgcaactgac
1441 taatcagcaa cgctatgtgc ttaaaataca ccttaaagac tgggaaggga atgaggctta
1501 ctcattgtat gaacatttct atctctcaag tgaagaactc aattatagga ttcaccttaa
1561 aggacttaca gggacagccg gcaaaataag cagcatcagc caaccaggaa atgattttag
1621 cacaaaggat ggagacaacg acaaatgtat ttgcaaatgt tcacaaatgc taacaggagg
1681 ctggtggttt gatgcatgtg gtccttccaa cttgaacgga atgtactatc cacagaggca
1741 gaacacaaat aagttcaacg gcattaaatg gtactactgg aaaggctcag gctattcgct
1801 caaggccaca accatgatga tccgaccagc agatttctaa acatcccagt ccacctgagg
1861 aactgtctcg aactattttc aaagacttaa gcccagtgca ctgaaagtca cggctgcgca
1921 ctgtgtcctc ttccaccaca gagggcgtgt gctcggtgct gacgggaccc acatgctcca
1981 gattagagcc tgtaaacttt atcacttaaa cttgcatcac ttaacggacc aaagcaagac
2041 cctaaacatc cataattgtg attagacaga acacctatgc aaagatgaac ccgaggctga
2101 gaatcagact gacagtttac agacgctgct gtcacaacca agaatgttat gtgcaagttt
2161 atcagtaaat aactggaaaa cagaacactt atgttataca atacagatca tcttggaact
2221 gcattcttct gagcactgtt tatacactgt gtaaataccc atatgtcct (SEQ ID
NO:103)
```

FIGURE 55A

Tie2 ligand2 (NM_001147)

MWQIVFFTLSCDLVLAAAYNNFRKSMDSIGKKQYQVQHGSCSYT

FLLPEMDNCRSSSSPYVSNAVQRDAPLEYDDSVQRLQVLENIMENNTQWLMKLENYIQ

DNMKKEMVEIQQNAVQNQTAVMIEIGTNLLNQTAEQTRKLTDVEAQVLNQTTRLELQL

LEHSLSTNKLEKQILDQTSEINKLQDKNSFLEKKVLAMEDKHIIQLQSIKEEKDQLQV

LVSKQNSIIEELEKKIVTATVNNSVLQKQQHDLMETVNNLLTMMSTSNSAKDPTVAKE

EQISFRDCAEVFKSGHTTNGIYTLTFPNSTEEIKAYCDMEAGGGGWTIIQRREDGSVD

FQRTWKEYKVGFGNPSGEYWLGNEFVSQLTNQQRYVLKIHLKDWEGNEAYSLYEHFYL

SSEELNYRIHLKGLTGTAGKISSISQPGNDFSTKDGDNDKCICKCSQMLTGGWWFDAC

GPSNLNGMYYPQRQNTNKFNGIKWYYWKGSGYSLKATTMMIRPADF (SEQ ID NO:104)

FIGURE 55B

VEGFC (NM_005429)

```
   1 cggggaaggg gagggaggag ggggacgagg gctctggcgg gtttggaggg gctgaacatc
  61 gcggggtgtt ctggtgtccc ccgccccgcc tctccaaaaa gctacaccga cgcggaccgc
 121 ggcggcgtcc tccctcgccc tcgcttcacc tcgcgggctc cgaatgcggg gagctcggat
 181 gtccggtttc ctgtgaggct tttacctgac acccgccgcc tttccccggc actggctggg
 241 agggcgccct gcaaagttgg gaacgcggag ccccggaccc gctcccgccg cctccggctc
 301 gcccaggggg ggtcgccggg aggagcccgg gggagaggga ccaggagggg cccgcggcct
 361 cgcaggggcg cccgcgcccc caccctgcc cccgccagcg gaccggtccc ccacccccgg
 421 tccttccacc atgcacttgc tgggcttctt ctctgtggcg tgttctctgc tcgccgctgc
 481 gctgctcccg ggtcctcgcg aggcgcccgc cgccgccgcc gccttcgagt ccggactcga
 541 cctctcggac gcggagcccg acgcgggcga ggccacggct tatgcaagca aagatctgga
 601 ggagcagtta cggtctgtgt ccagtgtaga tgaactcatg actgtactct acccagaata
 661 ttggaaaatg tacaagtgtc agctaaggaa aggaggctgg caacataaca gagaacaggc
 721 caacctcaac tcaaggacag aagagactat aaaatttgct gcagcacatt ataatacaga
 781 gatcttgaaa agtattgata atgagtggag aaagactcaa tgcatgccac gggaggtgtg
 841 tatagatgtg gggaaggagt ttggagtcgc gacaaacacc ttctttaaac ctccatgtgt
 901 gtccgtctac agatgtgggg gttgctgcaa tagtgagggg ctgcagtgca tgaacaccag
 961 cacgagctac ctcagcaaga cgttatttga aattacagtg cctctctctc aaggccccaa
1021 accagtaaca atcagttttg ccaatcacac ttcctgccga tgcatgtcta aactggatgt
1081 ttacagacaa gttcattcca ttattagacg ttccctgcca gcaacactac cacagtgtca
1141 ggcagcgaac aagacctgcc ccaccaatta catgtggaat aatcacatct gcagatgcct
1201 ggctcaggaa gattttatgt tttcctcgga tgctggagat gactcaacag atggattcca
1261 tgacatctgt ggaccaaaca aggagctgga tgaagagacc tgtcagtgtg tctgcagagc
1321 ggggcttcgg cctgccagct gtggacccca caaagaacta gacagaaact catgccagtg
1381 tgtctgtaaa aacaaactct tccccagcca atgtggggcc aaccgagaat ttgatgaaaa
1441 cacatgccag tgtgtatgta aaagaacctg ccccagaaat caacccctaa atcctggaaa
1501 atgtgcctgt gaatgtacag aaagtccaca gaaatgcttg ttaaaaggaa agaagttcca
1561 ccaccaaaca tgcagctgtt acagacggcc atgtacgaac cgccagaagg cttgtgagcc
1621 aggattttca tatagtgaag aagtgtgtcg ttgtgtccct tcatattgga aaagaccaca
1681 aatgagctaa gattgtactg ttttccagtt catcgatttt ctattatgga aaactgtgtt
1741 gccacagtag aactgtctgt gaacagagag acccttgtgg gtccatgcta acaaagacaa
1801 aagtctgtct ttcctgaacc atgtggataa ctttacagaa atggactgga gctcatctgc
1861 aaaaggcctc ttgtaaagac tggttttctg ccaatgacca aacagccaag attttcctct
1921 tgtgatttct ttaaaagaat gactatataa tttatttcca ctaaaaatat tgtttctgca
1981 ttcatttta tagcaacaac aattggtaaa actcactgtg atcaatattt ttatatcatg
2041 caaaatatgt ttaaaataaa atgaaaattg tattat (SEQ ID NO:105)
```

FIGURE 56A

VEGFC (NM_005429)

MHLLGFFSVACSLLAAALLPGPREAPAAAAAFESGLDLSDAEPD

AGEATAYASKDLEEQLRSVSSVDELMTVLYPEYWKMYKCQLRKGGWQHNREQANLNSR

TEETIKFAAAHYNTEILKSIDNEWRKTQCMPREVCIDVGKEFGVATNTFFKPPCVSVY

RCGGCCNSEGLQCMNTSTSYLSKTLFEITVPLSQGPKPVTISFANHTSCRCMSKLDVY

RQVHSIIRRSLPATLPQCQAANKTCPTNYMWNNHICRCLAQEDFMFSSDAGDDSTDGF

HDICGPNKELDEETCQCVCRAGLRPASCGPHKELDRNSCQCVCKNKLFPSQCGANREF

DENTCQCVCKRTCPRNQPLNPGKCACECTESPQKCLLKGKKFHHQTCSCYRRPCTNRQ

KACEPGFSYSEEVCRCVPSYWKRPQMS (SEQ ID NO:106)

FIGURE 56B

tPA(NM_000930)

```
   1 atggccctgt ccactgagca tcctcccgcc acacagaaac ccgcccagcc ggggccaccg
  61 accccacccc ctgcctggaa acttaaggag gccggagctg tggggagctc agagctgaga
 121 tcctacagga gtccagggct ggagagaaaa cctctgcgag gaaagggaag gagcaagccg
 181 tgaatttaag ggacgctgtg aagcaatcat ggatgcaatg aagagagggc tctgctgtgt
 241 gctgctgctg tgtggagcag tcttcgtttc gcccagccag gaaatccatg cccgattcag
 301 aagaggagcc agatcttacc aagtgatctg cagagatgaa aaaacgcaga tgatatacca
 361 gcaacatcag tcatggctgc gccctgtgct cagaagcaac cgggtggaat attgctggtg
 421 caacagtggc agggcacagt gccactcagt gcctgtcaaa agttgcagcg agccaaggtg
 481 tttcaacggg ggcacctgcc agcaggccct gtacttctca gatttcgtgt gccagtgccc
 541 cgaaggattt gctgggaagt gctgtgaaat agataccagg gccacgtgct acgaggacca
 601 gggcatcagc tacaggggca cgtggagcac agcggagagt ggcgccgagt gcaccaactg
 661 gaacagcagc gcgttggccc agaagcccta cagcgggcgg aggccagacg ccatcaggct
 721 gggcctgggg aaccacaact actgcagaaa cccagatcga gactcaaagc cctggtgcta
 781 cgtctttaag gcggggaagt acagctcaga gttctgcagc acccctgcct gctctgaggg
 841 aaacagtgac tgctactttg ggaatgggtc agcctaccgt ggcacgcaca gcctcaccga
 901 gtcgggtgcc tcctgcctcc cgtggaattc catgatcctg ataggcaagg tttacacagc
 961 acagaacccc agtgcccagg cactgggcct gggcaaacat aattactgcc ggaatcctga
1021 tggggatgcc aagccctggt gccacgtgct gaagaaccgc aggctgacgt gggagtactg
1081 tgatgtgccc tcctgctcca cctgcggcct gagacagtac agccagcctc agtttcgcat
1141 caaaggaggg ctcttcgccg acatcgcctc ccacccctgg caggctgcca tctttgccaa
1201 gcacaggagg tcgcccggag agcggttcct gtgcgggggc atactcatca gctcctgctg
1261 gattctctct gccgcccact gcttccagga gaggtttccg ccccaccacc tgacggtgat
1321 cttgggcaga acataccggg tggtccctgg cgaggaggag cagaaatttg aagtcgaaaa
1381 atacattgtc cataaggaat tcgatgatga cacttacgac aatgacattg cgctgctgca
1441 gctgaaatcg gattcgtccc gctgtgccca ggagagcagc gtggtccgca ctgtgtgcct
1501 tcccccggcg gacctgcagc tgccggactg gacggagtgt gagctctccg gctacggcaa
1561 gcatgaggcc ttgtctcctt tctattcgga gcggctgaag gaggctcatg tcagactgta
1621 cccatccagc cgctgcacat cacaacattt acttaacaga acagtcaccg acaacatgct
1681 gtgtgctgga gacactcgga gcggcgggcc ccaggcaaac ttgcacgacg cctgccaggg
1741 cgattcggga ggccccctgg tgtgtctgaa cgatggccgc atgactttgg tgggcatcat
1801 cagctggggc ctgggctgtg gacagaagga tgtcccgggt gtgtacacca aggttaccaa
1861 ctacctagac tggattcgtg acaacatgcg accgtgacca ggaacacccg actcctcaaa
1921 agcaaatgag atcccgcctc ttcttcttca gaagacactg caaaggcgca gtgcttctct
1981 acagacttct ccagacccac cacaccgcag aagcgggacg agaccctaca ggagagggaa
2041 gagtgcattt tcccagatac ttcccatttt ggaagttttc aggacttggt ctgatttcag
2101 gatactctgt cagatgggaa gacatgaatg cacactagcc tctccaggaa tgcctcctcc
2161 ctgggcagaa agtggccatg ccaccctgtt ttcagctaaa gcccaacctc ctgacctgtc
2221 accgtgagca gctttggaaa caggaccaca aaaatgaaag catgtctcaa tagtaaaaga
2281 taacaagatc tttcaggaaa gacggattgc attagaaata gacagtatat ttatagtcac
2341 aagagcccag cagggcctca aagttggggc aggctggctg gcccgtcatg ttcctcaaaa
2401 gcacccttga cgtcaagtct ccttcccctt tccccactcc ctggctctca gaaggtattc
2461 cttttgtgta cagtgtgtaa agtgtaaatc ctttttcttt ataaacttta gagtagcatg
2521 agagaattgt atcatttgaa caactaggct tcagcatatt tatagcaatc catgttagtt
2581 tttactttct gttgccacaa ccctgtttta tactgtactt aataaattca gatatatttt
2641 tcacagtttt tcc (SEQ ID NO:107)
```

FIGURE 57A

tPA(NM_000930)

MDAMKRGLCCVLLLCGAVFVSPSQEIHARFRRGARSYQVICRDE

KTQMIYQQHQSWLRPVLRSNRVEYCWCNSGRAQCHSVPVKSCSEPRCFNGGTCQQALY

FSDFVCQCPEGFAGKCCEIDTRATCYEDQGISYRGTWSTAESGAECTNWNSSALAQKP

YSGRRPDAIRLGLGNHNYCRNPDRDSKPWCYVFKAGKYSSEFCSTPACSEGNSDCYFG

NGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKP

WCHVLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQAAIFAKHRR

SPGERFLCGGILISSCWILSAAHCFQERFPPHHLTVILGRTYRVVPGEEEQKFEVEKY

IVHKEFDDDTYDNDIALLQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSGYG

KHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDA

CQGDSGGPLVCLNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNMRP (SEQ ID NO:108)

FIGURE 57B

Thrombomodulin (NM_000361)

```
   1 cttgcaatcc aggctttcct tggaagtggc tgtaacatgt atgaaaagaa agaaaggagg
  61 accaagagat gaaagagggc tgcacgcgtg ggggcccgag tggtgggcgg ggacagtcgt
 121 cttgttacag gggtgctggc cttccctggc gcctgcccct gtcggccccg cccgagaacc
 181 tccctgcgcc agggcagggt ttactcatcc cggcgaggtg atcccatgcg cgagggcggg
 241 cgcaagggcg gccagagaac ccagcaatcc gagtatgcgg catcagccct tcccaccagg
 301 cacttccttc cttttcccga acgtccaggg agggagggcc gggcacttat aaactcgagc
 361 cctggccgat ccgcatgtca gaggctgcct cgcaggggct gcgcgcacgg caagaagtgt
 421 ctgggctggg acggacagga gaggctgtcg ccatcggcgt cctgtgcccc tctgctccgg
 481 cacggccctg tcgcagtgcc cgcgctttcc ccggcgcctg cacgcggcgc gcctgggtaa
 541 catgcttggg gtcctggtcc ttggcgcgct ggccctggcc ggcctggggt tccccgcacc
 601 cgcagagccg cagccgggtg gcagccagtg cgtcgagcac gactgcttcg cgctctaccc
 661 gggccccgcg accttcctca atgccagtca gatctgcgac ggactgcggg gccacctaat
 721 gacagtgcgc tcctcggtgg ctgccgatgt catttccttg ctactgaacg gcgacggcgg
 781 cgttggccgc cggcgcctct ggatcggcct gcagctgcca cccggctgcg gcgaccccaa
 841 gcgcctcggg cccctgcgcg gcttccagtg ggttacggga gacaacaaca ccagctatag
 901 caggtgggca cggctcgacc tcaatggggc tcccctctgc ggcccgttgt gcgtcgctgt
 961 ctccgctgct gaggccactg tgcccagcga gccgatctgg gaggagcagc agtgcgaagt
1021 gaaggccgat ggcttcctct gcgagttcca cttcccagcc acctgcaggc cactggctgt
1081 ggagcccggc gccgcggctg ccgccgtctc gatcacctac ggcaccccgt tcgcggcccg
1141 cggagcggac ttccaggcgc tgccggtggg cagctccgcc gcggtggctc ccctcggctt
1201 acagctaatg tgcaccgcgc cgcccggagc ggtccagggg cactgggcca gggaggcgcc
1261 gggcgcttgg gactgcagcg tggagaacgg cggctgcgag cacgcgtgca atgcgatccc
1321 tggggctccc cgctgccagt gcccagccgg cgccgccctg caggcagacg ggcgctcctg
1381 caccgcatcc gcgacgcagt cctgcaacga cctctgcgag cacttctgcg ttcccaaccc
1441 cgaccagccg ggctcctact cgtgcatgtg cgagaccggc taccggctgg cggccgacca
1501 acaccggtgc gaggacgtgg atgactgcat actggagccc agtccgtgtc cgcagcgctg
1561 tgtcaacaca cagggtggct tcgagtgcca ctgctaccct aactacgacc tggtggacgg
1621 cgagtgtgtg gagcccgtgg acccgtgctt cagagccaac tgcgagtacc agtgccagcc
1681 cctgaaccaa actagctacc tctgcgtctg cgccgagggc ttcgcgccca ttccccacga
1741 gccgcacagg tgccagatgt tttgcaacca gactgcctgt ccagccgact gcgaccccaa
1801 cacccaggct agctgtgagt gccctgaagg ctacatcctg gacgacggtt tcatctgcac
1861 ggacatcgac gagtgcgaaa acggcggctt ctgctccggg gtgtgccaca acctccccgg
1921 taccttcgag tgcatctgcg ggccccgactc ggcccttgcc cgccacattg gcaccgactg
1981 tgactccggc aaggtggacg gtggcgacag cggctctggc gagcccccgc ccagcccgac
2041 gcccggctcc accttgactc ctccggccgt ggggctcgtg cattcgggct tgctcatagg
2101 catctccatc gcgagcctgt gcctggtggt ggcgcttttg gcgctcctct gccacctgcg
2161 caagaagcag ggcgccgcca gggccaagat ggagtacaag tgcgcggccc cttccaagga
2221 ggtagtgctg cagcacgtgc ggaccgagcg gacgccgcag agactctgag cggcctccgt
2281 ccaggagcct ggctccgtcc aggagctgtg cctcctcacc cccagctttg ctaccaaagc
2341 accttagctg gcattacagc tggagaagac cctccccgca ccccccaagc tgttttcttc
2401 tattccatgg ctaactggcg agggggtgat tagagggagg agaatgagcc tcggcctctt
2461 ccgtgacgtc actggaccac tgggcaatga tggcaatttt gtaacgaaga cacagactgc
2521 gatttgtccc aggtcctcac taccgggcgc aggagggtga gcgttattgg tcggcagcct
2581 tctgggcaga ccttgacctc gtgggctagg gatgactaaa atatttattt tttttaagta
2641 tttaggtttt tgtttgtttc ctttgttctt acctgtatgt ctccagtatc cactttgcac
2701 agctctccgg tctctctctc tctacaaact cccacttgtc atgtgacagg taaactatct
2761 tggtgaattt ttttttccta gccctctcac atttatgaag caagccccac ttattcccca
2821 ttcttcctag ttttctcctc ccaggaactg ggccaactca cctgagtcac cctacctgtg
2881 cctgacccta cttcttttgc tcatctagct gtctgctcag acagaacccc tacatgaaac
2941 agaaacaaaa acactaaaaa taaaaatggc catttgcttt ttcaccagat ttgctaattt
3001 atcctgaaat ttcagattcc cagagcaaaa taattttaaa caaagggttg agatgtaaaa
3061 ggtattaaat tgatgttgct ggactgtcat agaaattaca cccaaagagg tatttatctt
3121 tacttttaaa cagtgagcct gaattttgtt gctgttttga tttgtactga aaaatggtaa
3181 ttgttgctaa tcttcttatg caatttcctt ttttgttatt attacttatt tttgacagtg
3241 ttgaaaatgt tcagaaggtt gctctagatt gagagaagag acaaacacct cccaggagac
3301 agttcaagaa agcttcaaac tgcatgattc atgccaatta gcaattgact gtcactgttc
```

FIGURE 58A

```
3361 cttgtcactg gtagaccaaa ataaaaccag ctctactggt cttgtggaat tgggagcttg
3421 ggaatggatc ctggaggatg cccaattagg gcctagcctt aatcaggtcc tcagagaatt
3481 tctaccattt cagagaggcc ttttggaatg tggcccctga acaagaattg gaagctgccc
3541 tgcccatggg agctggttag aaatgcagaa tcctaggctc caccccatcc agttcatgag
3601 aatctatatt taacaagatc tgcaggggt gtgtctgctc agtaatttga ggacaaccat
3661 tccagactgc ttccaatttt ctggaataca tgaaatatag atcagttata agtagcaggc
3721 caagtcaggc ccttattttc aagaaactga ggaattttct ttgtgtagct ttgctctttg
3781 gtagaaaagg ctaggtacac agctctagac actgccacac agggtctgca aggtctttgg
3841 ttcagctaag ctaggaatga aatcctgctt cagtgtatgg aaataaatgt atcatagaaa
3901 tgtaactttt gtaagacaaa ggttttcctc ttctattttg taaactcaaa atatttgtac
3961 atagttattt atttattgga gataatctag aacacaggca aaatccttgc ttatgacatc
4021 acttgtacaa aataaacaaa taacaatgtg (SEQ ID NO:109)
```

FIGURE 58B

Thrombomodulin (NM_000361)

MLGVLVLGALALAGLGFPAPAEPQPGGSQCVEHDCFALYPGPAT

FLNASQICDGLRGHLMTVRSSVAADVISLLLNGDGGVGRRRLWIGLQLPPGCGDPKRL

GPLRGFQWVTGDNNTSYSRWARLDLNGAPLCGPLCVAVSAAEATVPSEPIWEEQQCEV

KADGFLCEFHFPATCRPLAVEPGAAAAAVSITYGTPFAARGADFQALPVGSSAAVAPL

GLQLMCTAPPGAVQGHWAREAPGAWDCSVENGGCEHACNAIPGAPRCQCPAGAALQAD

GRSCTASATQSCNDLCEHFCVPNPDQPGSYSCMCETGYRLAADQHRCEDVDDCILEPS

PCPQRCVNTQGGFECHCYPNYDLVDGECVEPVDPCFRANCEYQCQPLNQTSYLCVCAE

GFAPIPHEPHRCQMFCNQTACPADCDPNTQASCECPEGYILDDGFICTDIDECENGGF

CSGVCHNLPGTFECICGPDSALARHIGTDCDSGKVDGGDSGSGEPPPSPTPGSTLTPP

AVGLVHSGLLIGISIASLCLVVALLALLCHLRKKQGAARAKMEYKCAAPSKEVVLQHV

RTERTPQRL (SEQ ID NO:110)

FIGURE 58C

TF (NM_001993)

```
   1 aagactgcga gctccccgca ccccctcgca ctccctctgg ccggcccagg gcgccttcag
  61 cccaacctcc ccagccccac gggcgccacg gaacccgctc gatctcgccg ccaactggta
 121 gacatggaga cccctgcctg gccccgggtc ccgcgccccg agaccgccgt cgctcggacg
 181 ctcctgctcg gctgggtctt cgcccaggtg gccggcgctt caggcactac aaatactgtg
 241 gcagcatata atttaacttg gaaatcaact aatttcaaga caattttgga gtgggaaccc
 301 aaacccgtca atcaagtcta cactgttcaa ataagcacta agtcaggaga ttggaaaagc
 361 aaatgctttt acacaacaga cacagagtgt gacctcaccg acgagattgt gaaggatgtg
 421 aagcagacgt acttggcacg ggtcttctcc tacccggcag ggaatgtgga gagcaccggt
 481 tctgctgggg agcctctgta tgagaactcc ccagagttca caccttacct ggagacaaac
 541 ctcggacagc caacaattca gagttttgaa caggtgggaa caaaagtgaa tgtgaccgta
 601 gaagatgaac ggactttagt cagaaggaac aacactttcc taagcctccg ggatgttttt
 661 ggcaaggact taatttatac actttattat tggaaatctt caagttcagg aaagaaaaca
 721 gccaaaacaa acactaatga gtttttgatt gatgtggata aaggagaaaa ctactgtttc
 781 agtgttcaag cagtgattcc ctcccgaaca gttaaccgga agagtacaga cagcccggta
 841 gagtgtatgg gccaggagaa aggggaattc agagaaatat tctacatcat tggagctgtg
 901 gtatttgtgg tcatcatcct tgtcatcatc ctggctatat ctctacacaa gtgtagaaag
 961 gcaggagtgg ggcagagctg gaaggagaac tccccactga atgtttcata aaggaagcac
1021 tgttggagct actgcaaatg ctatattgca ctgtgaccga gaacttttaa gaggatagaa
1081 tacatggaaa cgcaaatgag tatttcggag catgaagacc ctggagttca aaaaactctt
1141 gatatgacct gttattacca ttagcattct ggttttgaca tcagcattag tcactttgaa
1201 atgtaacgaa tggtactaca accaattcca agttttaatt tttaacacca tggcaccttt
1261 tgcacataac atgctttaga ttatatattc cgcacttaag gattaaccag gtcgtccaag
1321 caaaaacaaa tgggaaaatg tcttaaaaaa tcctgggtgg acttttgaaa agctttttt
1381 ttttttttt tttgagacgg agtcttgctc tgttgcccag gctggagtgc agtagcacga
1441 tctcggctca cttgcaccct ccgtctctcg ggttcaagca attgtctgcc tcagcctccc
1501 gagtagctgg gattacaggt gcgcactacc acgccaagct aatttttgta ttttttagta
1561 gagatggggt ttcaccatct tggccaggct ggtcttgaat tcctgacctc agtgatccac
1621 ccaccttggc ctcccaaaga tgctagtatt atgggcgtga accaccatgc ccagccgaaa
1681 agcttttgag gggctgactt caatccatgt aggaaagtaa aatggaagga aattgggtgc
1741 atttctagga cttttctaac atatgtctat aatatagtgt ttaggttctt tttttttca
1801 ggaatacatt tggaaattca aaacaattgg gcaaactttg tattaatgtg ttaagtgcag
1861 gagacattgg tattctgggc agcttcctaa tatgctttac aatctgcact ttaactgact
1921 taagtggcat taaacatttg agagctaact atatttttat aagactacta tacaaactac
1981 agagtttatg atttaaggta cttaaagctt ctatggttga cattgtatat ataatttttt
2041 aaaaaggttt ttctatatgg ggattttcta tttatgtagg taatattgtt ctatttgtat
2101 atattgagat aatttattta atatacttta aataaaggtg actgggaatt gtt (SEQ ID
NO:111)
```

FIGURE 59A

TF (NM_001993)

METPAWPRVPRPETAVARTLLLGWVFAQVAGASGTTNTVAAYNL

TWKSTNFKTILEWEPKPVNQVYTVQISTKSGDWKSKCFYTTDTECDLTDEIVKDVKQT

YLARVFSYPAGNVESTGSAGEPLYENSPEFTPYLETNLGQPTIQSFEQVGTKVNVTVE

DERTLVRRNNTFLSLRDVFGKDLIYTLYYWKSSSSGKKTAKTNTNEFLIDVDKGENYC

FSVQAVIPSRTVNRKSTDSPVECMGQEKGEFREIFYIIGAVVFVVIILVIILAISLHK

CRKAGVGQSWKENSPLNVS (SEQ ID NO:112)

FIGURE 59B

GPR4 (NM_005282)

```
   1 ctggtgacct tacttatctc tgttgctttc tggggtccta ggaaatgcca gcactcccac
  61 ccacattgcc tgaactttcc aacactccct agctgcgctg tgtcctatct caacacttcc
 121 tcatgtattt cttgtgtctt ctagaacatt cccccgccat tattacttca atatggctac
 181 acatacttcc taattgccct gcaaaccatc tccttctcac cattgcccag cgatgctttc
 241 gtctcctcca taaacactcc cggagaccaa tttttgtgtc acccccatac tccctcgttg
 301 acacactgac tccatacata acctccttga aaaacctctt tattaatctc accatcctcc
 361 agacttccct cctgtcataa ttccatccct cctccaactt ttccctctca agctctgccc
 421 ttcccagccc agcccagcct acccaacctc atctcttccc tgtagaccac atcccaccat
 481 gttcccctga gcctccaagg aaggggctca gggggcccca tggcctcccg ctccctgtgg
 541 ccccacagcc cccgtgggcc aggggaagcg ccccagaagc cgaagtgccc accatgggca
 601 accacacgtg ggagggctgc cacgtggact cgcgcgtgga ccacctcttt ccgccatccc
 661 tctacatctt tgtcatcggc gtggggctgc ccaccaactg cctggctctg tgggcggcct
 721 accgccaggt gcaacagcgc aacgagctgg gcgtctacct gatgaacctc agcatcgccg
 781 acctgctgta catctgcacg ctgccgctgt gggtggacta cttcctgcac cacgacaact
 841 ggatccacgg ccccgggtcc tgcaagctct ttgggttcat cttctacacc aatatctaca
 901 tcagcatcgc cttcctgtgc tgcatctcgg tggaccgcta cctggctgtg gcccacccac
 961 tccgcttcgc ccgcctgcgc cgcgtcaaga ccgccgtggc cgtgagctcc gtggtctggg
1021 ccacggagct gggcgccaac tcggcgcccc tgttccatga cgagctcttc cgagaccgct
1081 acaaccacac cttctgcttt gagaagttcc ccatggaagg ctgggtggcc tggatgaacc
1141 tctatcgggt gttcgtgggc ttcctcttcc cgtgggcgct catgctgctg tcgtaccggg
1201 gcatcctgcg ggccgtgcgg ggcagcgtgt ccaccgagcg ccaggagaag gccaagatca
1261 agcggctggc cctcagcctc atcgccatcg tgctggtctg ctttgcgccc tatcacgtgc
1321 tcttgctgtc ccgcagcgcc atctacctgg gccgcccctg ggactgcggc ttcgaggagc
1381 gcgtcttttc tgcataccac agctcactgg ctttcaccag cctcaactgt gtggcggacc
1441 ccatcctcta ctgcctggtc aacgagggcg cccgcagcga tgtggccaag gccctgcaca
1501 acctgctccg ctttctggcc agcgacaagc cccaggagat ggccaatgcc tcgctcaccc
1561 tggagacccc actcacctcc aagaggaaca gcacagccaa agccatgact ggcagctggg
1621 cggccactcc gccctcccag ggggaccagg tgcagctgaa gatgctgccg ccagcacaat
1681 gaaccccgag tggcacagaa tccccagttt tcccctctca tcccacagtc ccttctctcc
1741 tggtctggtg tatgcaaatt gtatggaaaa agggctgtgt taatattcat aagaatacaa
1801 gaacttagga agagtgaggt tggtgtgtca ctggtcaacc tttgtgctcc cagatcccat
1861 cacagtttgg cgattgtgga gggcctcctg aaggaggaga tgagtaaata tatttttttg
1921 gagacagggt ctcactgtgt tgcccaggct ggagtgcagt agtgcagtcg tggctcactg
1981 cagcctccac ctcctgggct ctccagcgat cttcccacat cagcctcccg agtagctggg
2041 accacaaatg tgagcccacc catgcctggc taatttttgt acttttgta taaatggagt
2101 ctcactatgt ttccccaggc tgatcttgaa ctcctgggct caagagatcc tcctgccttg
2161 gcctcccaaa gtgctcagat tagagatgtg agccgccatg tctggccaga taaattaagt
2221 caaacatttg gtttccagaa aataaagaca aatagagaag gttagatttt ttttttcca
2281 acaagtggat aaaagtctgt gactcggggg aaagtggaag gagaaatgca gccgatatag
2341 agtcattatg tttgcaaagc ccctggtcat acaggccagg gaacataaga ccgcaattct
2401 aagtttctag ataaacagcg atctccaagt caagactgag gatgaagagg gagaatgtca
2461 gaactcaagt gaagggcaat cagggcagac tgcctggagg agtgatgcca gaaggtttgg
2521 gaagaaggtg tgggacaaga agaaagggta tttattcatt cattcaacag aggtttatgt
2581 agggcactgt gctgggtggg gctggggaca caacaatgac tgaggcagcc tggccttgcc
2641 ttcacagggc tcaccataca caagtaaata aaaaatatgt aatgtttgga attgct (SEQ
ID NO:113)
```

FIGURE 60A

GPR4 (NM_005282)

MGNHTWEGCHVDSRVDHLFPPSLYIFVIGVGLPTNCLALWAAYR

QVQQRNELGVYLMNLSIADLLYICTLPLWVDYFLHHDNWIHGPGSCKLFGFIFYTNIY

ISIAFLCCISVDRYLAVAHPLRFARLRRVKTAVAVSSVVWATELGANSAPLFHDELFR

DRYNHTFCFEKFPMEGWVAWMNLYRVFVGFLFPWALMLLSYRGILRAVRGSVSTERQE

KAKIKRLALSLIAIVLVCFAPYHVLLLSRSAIYLGRPWDCGFEERVFSAYHSSLAFTS

LNCVADPILYCLVNEGARSDVAKALHNLLRFLASDKPQEMANASLTLETPLTSKRNST

AKAMTGSWAATPPSQGDQVQLKMLPPAQ (SEQ ID NO:114)

FIGURE 60B

GPR66 (NM_006056)

```
   1 agcgggggggt tcccggccgg acaggcgggg cgtcggggcg cgggctgggg ccgctgtcag
  61 tcagtccact ggctcccgcg ccgcgtctgt gtccgtcgct cggagggtgg aagccggggt
 121 ctcgcgggcc gcgggccgca tgactcctct ctgcctcaat tgctctgtcc tccctggaga
 181 cctgtaccca gggggtgcaa ggaaccccat ggcttgcaat ggcagtgcgg ccaggggca
 241 ctttgaccct gaggacttga acctgactga cgaggcactg agactcaagt acctggggcc
 301 ccagcagaca gagctgttca tgcccatctg tgccacatac ctgctgatct tcgtggtggg
 361 cgctgtgggc aatgggctga cctgtctggt catcctgcgc cacaaggcca tgcgcacgcc
 421 taccaactac tacctcttca gcctggccgt gtcggacctg ctggtgctgc tggtgggcct
 481 gccctggag ctctatgaga tgtggcacaa ctacccctc ctgctgggcg ttggtggctg
 541 ctatttccgc acgctactgt ttgagatggt ctgcctggcc tcagtgctca acgtcactgc
 601 cctgagcgtg gaacgctatg tggccgtggt gcacccactc caggccaggt ccatggtgac
 661 gcgggcccat gtgcgccgag tgcttggggc cgtctggggt cttgccatgc tctgctccct
 721 gcccaacacc agcctgcacg gcatccagca gctgcacgtg ccctgccggg gcccagtgcc
 781 agactcagct gtttgcatgc tggtccgccc acgggccctc tacaacatgg tagtgcagac
 841 caccgcgctg ctcttcttct gcctgcccat ggccatcatg agcgtgctct acctgctcat
 901 tgggctgcga ctgcggcggg agaggctgct gctcatgcag gaggccaagg gcaggggctc
 961 tgcagcagcc aggtccagat acacctgcag gctccagcag cacgatcggg gccggagaca
1021 agtgaccaag atgctgtttg tcctggtcgt ggtgtttggc atctgctggg ccccgttcca
1081 cgccgaccgc gtcatgtgga gcgtcgtgtc acagtggaca gatggcctgc acctggcctt
1141 ccagcacgtg cacgtcatct ccggcatctt cttctacctg ggctcggcgg ccaaccccgt
1201 gctctatagc ctcatgtcca gccgcttccg agagaccttc caggaggccc tgtgcctcgg
1261 ggcctgctgc catcgcctca gaccccgcca cagctcccac agcctcagca ggatgaccac
1321 aggcagcacc ctgtgtgatg tgggctccct gggcagctgg gtccaccccc tggctgggaa
1381 cgatggccca gaggcgcagc aagagaccga tccatcctga gtggagcctt aaagtggctt
1441 cacctggagg ggccagaggg tcacctggag ctggggagac acatctgcct tcctctgcag
1501 ggatccttca cgtactgtcc ctagttcagc ctagaaattc tgaccagcac ctcagtttcc
1561 ctcagaggga aacagcagga ggagggatcc ctgactgctg aggactcaca ctgaccagac
1621 gccacacctt gtgcttctta tctgtccact gccactcccc cagttcaaat ccttaccctg
1681 cagaaatatc acagttagct ggggctcagc agtcctccct ctggggactc cctgccacca
1741 ctgccagttt ctgaaacggt cccactgggt cctcactgtc cttcccagtt cctgttcagg
1801 ttctggcagg ggcccaggga tccaggggac ctggttccaa tctcagccct gctgtcacca
1861 ccttgtcatg caccatcaag catatcagtc taccttttct tttttctgag acagagtctc
1921 actctgtcgc ccaggctaga gtgcagtggc gcgattttgg ctcactgcaa cctccgcctc
1981 cggggttcaa gcgattctcc tgcctcagcc tcccgagttg ctgggactac aggtgagccc
2041 cagcatgccc agctaatttt ttttaatttt tagtagagac ggggtttcac catgttggcc
2101 aggctggtct caaactcttg acctcaggtg atccgccgac ctcggcctcc caaagtcctc
2161 ggattacagg catgagccac cacacccggc caatcagtcc acctttctag gccttggttc
2221 cttgcctgaa aaatgaaaga ggcgctggct ttccacagtg tcatgctttg gcactttagc
2281 tatggttttc tttctgtgtg tgtgtaagcc actgcttata ataaaaccaa caataccctc
2341 agactgaaag ggcggaagtt attatctgca tctttatcaa ccccaagccc cacttcctcc
2401 ctgacctccc catgccctcc ccagcctctc ccagcacaag tggggcaaag ccagcatgca
2461 agcagacccc accaccacag cccacctccg tcctcacata cgtgcaggct ggctcgggag
2521 tccagtgagc agagcattgg acttggctgg ccagagggtc tctgagggca agagacatgg
2581 ccaaccaagg gcaaggagtg accctgtgga gggttctgcc gaactcaatg cagtgagaag
2641 agggacaggg acaagtagtc cttgaaactg agccccattc tgaatccctg caggccaagt
2701 cattgctcag ccaggactca gttcatgggg gaaacttgac ctgctgcagt ccctgagtct
2761 tgtcctcctg agaggaagcc ctggcttcca aggctgggag ctggaggatg accttcggtc
2821 ggtctgtctg ggttctccct gcagacagct tcctagctca tgcccatagc tcatgctccc
2881 tgccgagaaa gtggaggacg tggtacaggg ttgcagatgt ttagttttaa aaattcaatt
2941 ataaaaataa taaatgctca tgatagaaaa tttggaaagt gcaaataagc aaaaatgaaa
3001 acaattttaa aaatgtaaaa cctctcttgc cagggaatgg gggaagggca agtgaggagt
3061 tctttaatgg gtgaagagtt tcagttttgc aaaatgaaaa agttctggag atcagttgtg
3121 caacaatatg aatatacata acaatactga actatacact gaaatggtta agatggtaca
3181 ttttatgtta tgtgtatttt accacaattt ttataaaaag aggattaaat ctaaaggaaa
3241 gaaaaaatta aaaccaccca taactttact ctgaagcagt aacagtggca tgtttcctcc
3301 taaaaaaaaa aaaaaaaaaa gaagaaaaaa aaataaagaa aaaaaaaaaa aaaa (SEQ ID
NO:115)
```

FIGURE 61A

GPR66 (NM_006056)

MTPLCLNCSVLPGDLYPGGARNPMACNGSAARGHFDPEDLNLTD

EALRLKYLGPQQTELFMPICATYLLIFVVGAVGNGLTCLVILRHKAMRTPTNYYLFSL

AVSDLLVLLVGLPLELYEMWHNYPFLLGVGGCYFRTLLFEMVCLASVLNVTALSVERY

VAVVHPLQARSMVTRAHVRRVLGAVWGLAMLCSLPNTSLHGIQQLHVPCRGPVPDSAV

CMLVRPRALYNMVVQTTALLFFCLPMAIMSVLYLLIGLRLRRERLLLMQEAKGRGSAA

ARSRYTCRLQQHDRGRRQVTKMLFVLVVVFGICWAPFHADRVMWSVVSQWTDGLHLAF

QHVHVISGIFFYLGSAANPVLYSLMSSRFRETFQEALCLGACCHRLRPRHSSHSLSRM

TTGSTLCDVGSLGSWVHPLAGNDGPEAQQETDPS (SEQ ID NO:116)

FIGURE 61B

SLC22A2 (NM_003058)

```
   1 ctttgaagtc agctggacca aggaaaggcc ctgccctgaa ggctggtcac ttgcagaggt
  61 aaactcccct ctttgacttc tggccagggt ttgtgctgag ctggctgcag ccgctctcag
 121 cctcgctccg ggcacgtcgg gcagcctcgg gccctcctgc ctgcaggatc atgcccacca
 181 ccgtggacga tgtcctggag catggagggg agtttcactt tttccagaag caaatgtttt
 241 tcctcttggc tctgctctcg gctaccttcg cgcccatcta cgtgggcatc gtcttcctgg
 301 gcttcacccc tgaccaccgc tgccggagcc ccggagtggc cgagctgagt ctgcgctgcg
 361 gctggagtcc tgcagaggaa ctgaactaca cggtgccggg cccaggacct gcgggcgaag
 421 cctccccaag acagtgtagg cgctacgagg tggactggaa ccagagcacc ttcgactgcg
 481 tggacccccc ggccagcctg gacaccaaca ggagccgcct gccactgggc ccctgccggg
 541 acggctgggt gtacgagacg cctggctcgt ccatcgtcac cgagtttaac ctggtatgtg
 601 ccaactcctg gatgttggac ctattccagt catcagtgaa tgtaggattc tttattggct
 661 ctatgagtat cggctacata gcagacaggt ttggccgtaa gctctgcctc ctaactacag
 721 tcctcataaa tgctgcagct ggagttctca tggccatttc cccaacctat acgtggatgt
 781 taatttttcg cttaatccaa ggactggtca gcaaagcagg ctggttaata ggctacatcc
 841 tgattacaga atttgttggg cggagatatc ggagaacagt ggggattttt taccaagttg
 901 cctatacagt tgggctcctg gtgctagctg gggtggctta cgcacttcct cactggaggt
 961 ggttgcagtt cacagttgct ctgcccaact tcttcttctt gctctattac tggtgcatac
1021 ctgagtctcc caggtggctg atctcccaga ataagaatgc tgaagccatg agaatcatta
1081 agcacatcgc aaagaaaaat ggaaaatctc tacccgcctc ccttcagcgc ctgagacttg
1141 aagaggaaac tggcaagaaa ttgaaccctt catttcttga cttggtcaga actcctcaga
1201 taaggaaaca tactatgata ttgatgtaca actggttcac gagctctgtg ctctaccagg
1261 gcctcatcat gcacatgggc cttgcaggtg acaatatcta cctggatttc ttctactctg
1321 ccctggttga attcccagct gccttcatga tcatcctcac catcgaccgc atcggacgcc
1381 gttacccttg ggctgcatca aatatggttg caggggcagc ctgtctggcc tcagttttta
1441 tacctggtga tctacaatgg ctaaaaatta ttatctcatg cttgggaaga atggggatca
1501 caatggccta tgagatagtc tgcctggtca atgctgagct gtaccccaca ttcattagga
1561 atcttggcgt ccacatctgt tcctcaatgt gtgacattgg tggcatcatc acgccattcc
1621 tggtctaccg gctcactaac atctggcttg agctcccgct gatggttttc ggcgtgcttg
1681 gcttggttgc tggaggtctg gtgctgttgc ttccagaaac taaagggaaa gctttgcctg
1741 agaccatcga ggaagccgaa aatatgcaaa gaccaagaaa aaataaagaa aagatgattt
1801 acctccaagt tcagaaacta gacattccat tgaactaaga agagagaccg ttgctgctgt
1861 catgacctag ctttgatggc agcaagacca aaagtagaaa tccctgcact catcacaaag
1921 cccatacaac tcaaccaaac ttacccctga gccctatcaa cctaggtcta cagccagtgg
1981 agtctattgt acactgtgga aaaataccca tgggaccaga tcctgccaaa ttcttccagc
2041 tcactttatt ctcagcattc ctaggacatt ggacattggt tttctggagg gttttttttc
2101 catctttgta ttttttaaa tttgattctt ttctttgcaa tgctatctaa ccagaataca
2161 taggggaact gtgggctagg caaacaaaat agaaaaaagt gtgaaaaaca gtaaagttgg
2221 gagaggagca tctatttttct taaagaaata aaacacccaa aacaatataa agttgtccag
2281 aatgtatgtc aagaatttta gataggcctt tcagtaacac aggtgaagaa atttttaaaa
2341 atacattgat tattatctag gttagactta aagtgaatct caaataaaag aatcaggaat
2401 acaacttaag tgatcatgag gtccttccat atttagattg ggtaagcatg aatgtgtatt
2461 ttctacaaaa gaccttgaga agagttcaat aaaaaatgtt agcattataa aa (SEQ ID
NO:117)
```

FIGURE 62A

SLC22A2 (NM_003058)

MPTTVDDVLEHGGEFHFFQKQMFFLLALLSATFAPIYVGIVFLG

FTPDHRCRSPGVAELSLRCGWSPAEELNYTVPGPGPAGEASPRQCRRYEVDWNQSTFD

CVDPLASLDTNRSRLPLGPCRDGWVYETPGSSIVTEFNLVCANSWMLDLFQSSVNVGF

FIGSMSIGYIADRFGRKLCLLTTVLINAAAGVLMAISPTYTWMLIFRLIQGLVSKAGW

LIGYILITEFVGRRYRRTVGIFYQVAYTVGLLVLAGVAYALPHWRWLQFTVALPNFFF

LLYYWCIPESPRWLISQNKNAEAMRIIKHIAKKNGKSLPASLQRLRLEEETGKKLNPS

FLDLVRTPQIRKHTMILMYNWFTSSVLYQGLIMHMGLAGDNIYLDFFYSALVEFPAAF

MIILTIDRIGRRYPWAASNMVAGAACLASVFIPGDLQWLKIIISCLGRMGITMAYEIV

CLVNAELYPTFIRNLGVHICSSMCDIGGIITPFLVYRLTNIWLELPLMVFGVLGLVAG

GLVLLLPETKGKALPETIEEAENMQRPRKNKEKMIYLQVQKLDIPLN (SEQ ID NO:118)

FIGURE 62B

NLSN1 (NM_002420)

```
   1 gccctggcca aggaggaggc tgaaagagcc tgagctgtgc cctctccatt ccactgctgt
  61 ggcagggtca gaaatcttgg atagagaaaa ccttttgcaa acgggaatgt atctttgtaa
 121 ttcctagcac gaaagactct aacaggtgtt gctgtggcca gttcaccaac cagcatatcc
 181 cccctctgcc aagtgcaaca cccagcaaaa atgaagagga aaacaaacag gtggagactc
 241 agcctgagaa atggtctgtt gccaagcaca cccagagcta cccaacagat tcctatggag
 301 ttcttgaatt ccagggtggc ggatattcca ataaagccat gtatatccgt gtatcctatg
 361 acaccaagcc agactcactg ctccatctca tggtgaaaga ttggcagctg gaactcccca
 421 agctcttaat atctgtgcat ggaggcctcc agaactttga gatgcagccc aagctgaaac
 481 aagtctttgg gaaaggcctg atcaaggctg ctatgaccac cggggcctgg atcttcaccg
 541 ggggtgtcag cacaggtgtt atcagccacg taggggatgc cttgaaagac cactcctcca
 601 agtccagagg ccgggtttgt gctataggaa ttgctccatg gggcatcgtg gagaataagg
 661 aagacctggt tggaaaggat gtaacaagag tgtaccagac catgtccaac cctctaagta
 721 agctctctgt gctcaacaac tcccacaccc acttcatcct ggctgacaat ggcaccctgg
 781 gcaagtatgg cgccgaggtg aagctgcgaa ggctgctgga aaagcacatc tccctccaga
 841 agatcaacac aagactgggg cagggcgtgc ccctcgtggg tctcgtggtg gaggggggcc
 901 ctaacgtggt gtccatcgtc ttggaatacc tgcaagaaga gcctcccatc cctgtggtga
 961 tttgtgatgg cagcggacgt gcctcggaca tcctgtcctt tgcgcacaag tactgtgaag
1021 aaggcggaat aataaatgag tccctcaggg agcagcttct agttaccatt cagaaaacat
1081 ttaattataa taaggcacaa tcacatcagc tgtttgcaat tataatggag tgcatgaaga
1141 agaaagaact cgtcactgtg ttcagaatgg gttctgaggg ccagcaggac atcgagatgg
1201 caattttaac tgccctgctg aaaggaacaa acgtatctgc tccagatcag ctgagcttgg
1261 cactggcttg gaaccgcgtg gacatagcac gaagccagat ctttgtcttt gggccccact
1321 ggccgccccc gggaagcctg gcacccccga cggacagcaa agccacggag aaggagaaga
1381 agccacccat ggccaccacc aagggaggaa gaggaaaagg gaaaggcaag aagaaaggga
1441 aagtgaaaga ggaagtggag gaagaaactg acccccggaa gatagagctg ctgaactggg
1501 tgaatgcttt ggagcaagcg atgctagatg ctttagtctt agatcgtgtc gactttgtga
1561 agctcctgat tgaaaacgga gtgaacatgc aacactttct gaccattccg aggctggagg
1621 agctttataa cacaagactg ggtccaccaa acacacttca tctgctggtg agggatgtga
1681 aaaagagcaa ccttccgcct gattaccaca tcagcctcat agacatcggg ctcgtgctgg
1741 agtacctcat gggaggagcc taccgctgca actacactcg gaaaaacttt cggacccttt
1801 acaacaactt gtttggacca aagaggccta aagctcttaa acttctggga atggaagatg
1861 atgagcctcc agctaaaggg aagaaaaaaa aaaaaaagaa aaaggaggaa gagatcgaca
1921 ttgatgtgga cgaccctgcc gtgagtcggt tccagtatcc cttccacgag ctgatggtgt
1981 gggcagtgct gatgaaacgc cagaaaatgg cagtgttcct ctggcagcga ggggaagaga
2041 gcatggccaa ggccctggtg gcctgcaagc tctacaaggc catggcccac gagtcctccg
2101 agagtgatct ggtggatgac atctcccagg acttggataa caattccaaa gacttcggcc
2161 agcttgcttt ggagttatta gaccagtcct ataagcatga cgagcagatc gctatgaaac
2221 tcctgaccta cgagctgaaa aactggagca actcgacctg cctcaaactg gccgtggcag
2281 ccaaacaccg ggacttcatt gctcacacct gcagccagat gctgctgacc gatatgtgga
2341 tgggaagact gcggatgcgg aagaaccccg gcctgaaggt tatcatgggg attcttctac
2401 cccccaccat cttgtttttg gaatttcgca catatgatga tttctcgtat caaacatcca
2461 aggaaaacga ggatggcaaa gaaaaagaag aggaaaatac ggatgcaaat gcagatgctg
2521 gctcaagaaa gggggatgag gagaacgagc ataaaaaaca gagaagtatt cccatcggaa
2581 caaagatctg tgaattctat aacgcgccca ttgtcaagtt ctggttttac acaatatcat
2641 acttgggcta cctgctgctg tttaactacg tcatcctggt gcggatggat ggctggccgt
2701 ccctccagga gtggatcgtc atctcctaca tcgtgagcct ggcgttagag aagatacgag
2761 agatcctcat gtcagaacca ggcaaactca gccagaaaat caaagtttgg cttcaggagt
2821 actggaacat cacagatctc gtggccattt ccacattcat gattggagca attcttcgcc
2881 tacagaacca gccctacatg ggctatggcc gggtgatcta ctgtgtggat atcatcttct
2941 ggtacatccg tgtcctggac atctttggtg tcaacaagta tctggggcca tacgtgatga
3001 tgattggaaa gatgatgatc gacatgctgt actttgtggt catcatgctg gtcgtgctca
3061 tgagtttcgg agtagcccgt caagccattc tgcatccaga ggagaagccc tcttggaaac
3121 tggcccgaaa catcttctac atgccctact ggatgatcta tggagaggtg tttgcagacc
3181 agatagacct ctacgccatg gaaattaatc ctccttgtgg tgagaaccta tatgatgagg
3241 agggcaagcg gcttcctccc tgtatccccg gcgcctggct cactccagca ctcatggcgt
3301 gctatctact ggtcgccaac atcctgctgg tgaacctgct gattgctgtg ttcaacaata
```

FIGURE 63A

3361 ccttctttga agtaaaatca atatccaacc aggtgtggaa gttccagcga tatcagctga
3421 ttatgacatt tcatgacagg ccagtcctgc ccccaccgat gatcatttta agccacatct
3481 acatcatcat tatgcgtctc agcggccgct gcaggaaaaa gagagaaggg gaccaagagg
3541 aacgggatcg tggattgaag ctcttcctta gcgacgagga gctaaagagg ctgcatgagt
3601 tcgaggagca gtgcgtgcag gagcacttcc gggagaagga ggatgagcag cagtcgtcca
3661 gcgacgagcg catccgggtc acttctgaaa gagttgaaaa tatgtcaatg aggttggaag
3721 aaatcaatga aagagaaact tttatgaaaa cttccctgca gactgttgac cttcgacttg
3781 ctcagctaga agaattatct aacagaatgg tgaatgctct tgaaaatctt gcgggaatcg
3841 acaggtctga cctgatccag gcacggtccc gggcttcttc tgaatgtgag gcaacgtatc
3901 ttctccggca aagcagcatc aatagcgctg atggctacag cttgtatcga tatcatttta
3961 acggagaaga gttattattt gaggatacat ctctctccac gtcaccaggg acaggagtca
4021 ggaaaaaaac ctgttccttc cgtataaagg aagagaagga cgtgaaaacg cacctagtcc
4081 cagaatgtca gaacagtctt caccttcac tgggcacaag cacatcagca accccagatg
4141 gcagtcacct tgcagtagat gacttaaaga acgctgaaga gtcaaaatta ggtccagata
4201 ttgggatttc aaaggaagat gatgaaagac agacagactc taaaaaagaa gaaactattt
4261 ccccaagttt aaataaaaca gatgtgatac atggacagga caaatcagat gttcaaaaca
4321 ctcagctaac agtggaaacg acaaatatag aaggcactat ttcctatccc ctggaagaaa
4381 ccaaaattac acgctatttc cccgatgaaa cgatcaatgc ttgtaaaaca atgaagtcca
4441 gaagcttcgt ctattcccgg ggaagaaagc tggtcggtgg ggttaaccag gatgtagagt
4501 acagttcaat cacggaccag caattgacga cggaatggca atgccaagtt caaaagatca
4561 cgcgctctca tagcacagat attccttaca ttgtgtcgga agctgcagtg caagctgagc
4621 ataaagagca gtttgcagat atgcaagatg aacaccatgt cgctgaagca attcctcgaa
4681 tccctcgctt gtccctaacc attactgaca gaaatgggat ggaaaactta ctgtctgtga
4741 agccagatca aactttggga ttcccatctc tcaggtcaaa aagtttacat ggacatccta
4801 ggaatgtgaa atccattcag ggaaagttag acagatctgg acatgccagt agtgtaagca
4861 gcttagtaat tgtgtctgga atgacagcag aagaaaaaaa ggttaagaaa gagaaagctt
4921 ccacagaaac tgaatgctag tctgttttgt ttctttaatt ttttttttta acagtcagaa
4981 ccactaatgg gtgtcatctt ggccatctaa acatcatcaa tttctaaaaa cattttccct
5041 taaaaaattt tggaaattca gacttgattt acaatttaat gcactaaaag tagtattttg
5101 ttagcatatg ttagtaggct tagtttttc agttgcagta gtatcaaatg aaagtgatga
5161 tactgtaacg aagataaatt ggctaatcag tatacaagat tatacaatct ctttattact
5221 gagggccacc aaatagccta ggaagtgccc tcgagcactg aagtcaccat taggtcactt
5281 aagaagtaag caactagctg ggcacagtgg ctcatgcctg taatcctagc actttgggag
5341 gccaaggcag aaagatagct tgagtccagg agtttgagac cagcctgggc aacatagtga
5401 taccccatct cttaaaaaaa aaaaaaaaaa a (SEQ ID NO:119)

FIGURE 63B

NLSN1 (NM_002420)

MYIRVSYDTKPDSLLHLMVKDWQLELPKLLISVHGGLQNFEMQP

KLKQVFGKGLIKAAMTTGAWIFTGGVSTGVISHVGDALKDHSSKSRGRVCAIGIAPWG

IVENKEDLVGKDVTRVYQTMSNPLSKLSVLNNSHTHFILADNGTLGKYGAEVKLRRLL

EKHISLQKINTRLGQGVPLVGLVVEGGPNVVSIVLEYLQEEPPIPVVICDGSGRASDI

LSFAHKYCEEGGIINESLREQLLVTIQKTFNYNKAQSHQLFAIIMECMKKKELVTVFR

MGSEGQQDIEMAILTALLKGTNVSAPDQLSLALAWNRVDIARSQIFVFGPHWPPLGSL

APPTDSKATEKEKKPPMATTKGGRGKGKGKKKGKVKEEVEEETDPRKIELLNWVNALE

QAMLDALVLDRVDFVKLLIENGVNMQHFLTIPRLEELYNTRLGPPNTLHLLVRDVKKS

NLPPDYHISLIDIGLVLEYLMGGAYRCNYTRKNFRTLYNNLFGPKRPKALKLLGMEDD

EPPAKGKKKKKKKKEEEIDIDVDDPAVSRFQYPFHELMVWAVLMKRQKMAVFLWQRGE

ESMAKALVACKLYKAMAHESSESDLVDDISQDLDNNSKDFGQLALELLDQSYKHDEQI

AMKLLTYELKNWSNSTCLKLAVAAKHRDFIAHTCSQMLLTDMWMGRLRMRKNPGLKVI

MGILLPPTILFLEFRTYDDFSYQTSKENEDGKEKEEENTDANADAGSRKGDEENEHKK

QRSIPIGTKICEFYNAPIVKFWFYTISYLGYLLLFNYVILVRMDGWPSLQEWIVISYI

VSLALEKIREILMSEPGKLSQKIKVWLQEYWNITDLVAISTFMIGAILRLQNQPYMGY

GRVIYCVDIIFWYIRVLDIFGVNKYLGPYVMMIGKMMIDMLYFVVIMLVVLMSFGVAR

QAILHPEEKPSWKLARNIFYMPYWMIYGEVFADQIDLYAMEINPPCGENLYDEEGKRL

PPCIPGAWLTPALMACYLLVANILLVNLLIAVFNNTFFEVKSISNQVWKFQRYQLIMT

FHDRPVLPPPMIILSHIYIIIMRLSGRCRKKREGDQEERDRGLKLFLSDEELKRLHEF

EEQCVQEHFREKEDEQQSSSDERIRVTSERVENMSMRLEEINERETFMKTSLQTVDLR

LAQLEELSNRMVNALENLAGIDRSDLIQARSRASSECEATYLLRQSSINSADGYSLYR

YHFNGEELLFEDTSLSTSPGTGVRKKTCSFRIKEEKDVKTHLVPECQNSLHLSLGTST

SATPDGSHLAVDDLKNAEESKLGPDIGISKEDDERQTDSKKEETISPSLNKTDVIHGQ

DKSDVQNTQLTVETTNIEGTISYPLEETKITRYFPDETINACKTMKSRSFVYSRGRKL

VGGVNQDVEYSSITDQQLTTEWQCQVQKITRSHSTDIPYIVSEAAVQAEHKEQFADMQ

DEHHVAEAIPRIPRLSLTITDRNGMENLLSVKPDQTLGFPSLRSKSLHGHPRNVKSIQ

GKLDRSGHASSVSSLVIVSGMTAEEKKVKKEKASTETEC (SEQ ID NO:120)

FIGURE 63C

ATN2 (Na/K transport, NM_000702)

```
   1 tctctgtctg ccagggtctc cgactgtccc agacgggctg gtgtgggctt gggatcctcc
  61 tggtgacctc tcccgctaag gtccctcagc cactctgccc caagatgggc cgtggggctg
 121 gccgtgagta ctcacctgcc gccaccacgg cagagaatgg gggcggcaag aagaaacaga
 181 aggagaagga actggatgag ctgaagaagg aggtggcaat ggatgaccac aagctgtcct
 241 tggatgagct gggccgcaaa taccaagtgg acctgtccaa gggcctcacc aaccagcggg
 301 ctcaggacgt tctggctcga gatgggccca acgccctcac accacctccc acaaccccctg
 361 agtgggtcaa gttctgccgt cagcttttcg gggggttctc catcctgctg tggattgggg
 421 ctatcctctg cttcctggcc tacggcatcc aggctgccat ggaggatgaa ccatccaacg
 481 acaatctata tctgggtgtg gtgctggcag ctgtggtcat tgtcactggc tgcttctcct
 541 actaccagga ggccaagagc tccaagatca tggattcctt caagaacatg gtacctcagc
 601 aagcccttgt gatccgggag ggagagaaga tgcagatcaa cgcagaggaa gtggtggtgg
 661 gagacctggt ggaggtgaag ggtggagacc gcgtccctgc tgacctccgg atcatctctt
 721 ctcatggctg taaggtggat aactcatcct taacaggaga gtcggagccc cagacccgct
 781 cccccgagtt cacccatgag aacccccctgg agacccgcaa tatctgtttc ttctccacca
 841 actgtgttga aggcactgcc aggggcattg tgattgccac aggagaccgg acggtgatgg
 901 gccgcatagc tactctcgcc tcaggcctgg aggttgggcg gacacccata gcaatggaga
 961 ttgaacactt catccagctg atcacagggg tcgctgtatt cctgggggtc tccttcttcg
1021 tgctctccct catcctgggc tacagctggc tggaggcagt catcttcctc atcggcatca
1081 tagtggccaa cgtgcctgag gggcttctgg ccactgtcac tgtgtgcctg accctgacag
1141 ccaagcgcat ggcacggaag aactgcctgg tgaagaacct ggaggcggtg gagacgctgg
1201 gctccacgtc caccatctgc tcggacaaga cgggcaccct cacccagaac cgcatgaccg
1261 tcgcccacat gtggttcgac aaccaaatcc atgaggctga caccaccgaa gatcagtctg
1321 gggccacttt tgacaaacga tcccctacgt ggacggccct gtctcgaatt gctggtctct
1381 gcaaccgcgc cgtcttcaag gcaggacagg agaacatctc cgtgtctaag cgggacacag
1441 ctggtgatgc ctctgagtca gctctgctca agtgcattga gctctcctgt ggctcagtga
1501 ggaaaatgag agacagaaac cccaaggtgg cagagattcc tttcaactct accaacaagt
1561 accagctgtc tatccacgag cgagaagaca gcccccagag ccacgtgctg gtgatgaagg
1621 gggccccaga gcgcattctg gaccggtgct ccaccatcct ggtgcagggc aaggagatcc
1681 cgctcgacaa ggagatgcaa gatgcctttc aaaatgccta catggagctg gggggacttg
1741 gggagcgtgt gctgggattc tgtcaactga atctgccatc tggaaagttt cctcggggct
1801 tcaaattcga cacggatgag ctgaactttc ccacggagaa gctttgcttt gtggggctca
1861 tgtctatgat tgaccctccc cgggctgctg tgccagatgc tgtgggcaag tgccgaagcg
1921 caggcatcaa ggtgatcatg gtaaccgggg atcaccctat cacagccaag gccattgcca
1981 aaggcgtggg catcatatca gagggtaacg agactgtgga ggacattgca gcccggctca
2041 acattcccat gagtcaagtc aaccccagag aagccaaggc atgcgtggtg cacggctctg
2101 acctgaagga catgacatcg gagcagctcg atgagatcct caagaaccac acagagatcg
2161 tctttgctcg aacgtctccc cagcagaagc tcatcattgt ggagggatgt cagaggcagg
2221 gagccattgt ggccgtgacg ggtgacgggg tgaacgactc ccctgcattg aagaaggctg
2281 acattggcat tgccatgggc atctctggct ctgacgtctc taagcaggca gccgacatga
2341 tcctgctgga tgacaacttt gcctccatcg tcacgggggt ggaggagggc cgcctgatct
2401 ttgacaactt gaagaaatcc atcgcctaca ccctgaccag caacatcccc gagatcaccc
2461 ccttcctgct gttcatcatt gccaacatcc ccctacctct gggcactgtg accatccttt
2521 gcattgacct gggcacagat atggtccctg ccatctcctt ggcctatgag gcagctgaga
2581 gtgatatcat gaagcggcag ccacgaaact cccagacgga caagctggtg aatgagaggc
2641 tcatcagcat ggcctacgga cagatcggga tgatccaggc actgggtggc ttcttcacct
2701 actttgtgat cctggcagag aacggtttcc tgccatcacg gctactggga atccgcctcg
2761 actgggatga ccggaccatg aatgatctgg aggacagcta tggacaggag tggacctatg
2821 agcagcggaa ggtggtggag ttcacgtgcc acacggcatt ctttgccagc atcgtggtgg
2881 tgcagtgggc tgacctcatc atctgcaaga cccgccgcaa ctcagtcttc cagcagggca
2941 tgaagaacaa gatcctgatt tttgggctcc tggaggagac ggcgttggct gcctttctct
3001 cttactgccc aggcatgggt gtagccctcc gcatgtaccc gctcaaagtc acctggtggt
3061 tctgcgcctt cccctacagc ctcctcatct tcatctatga tgaggtccga aagctcatcc
3121 tgcggcggta tcctggtggc tgggtggaga aggagacata ctactgaccc cattggaaga
3181 agaaccaggc atggaaagat ggggagctct ggaggtgttg tggggatggt gatggagagg
3241 gatggaaata acgggtggca ttgggtggca acatttgggg agagataatg aggcaactca
```

FIGURE 64A

3301 gcaggctaag ttgcggggta tataaattgg ggtgatgacc ccatagacct aactgtgaac
3361 aatcagatta gacactatgt gttagagtcc ccccgaccag atccttttcc atcccactcc
3421 actatgttgt ctatttttc tgaggaatta agggttaccc caccctgccc actcccatcc
3481 cttcaacccc acttcctact gtaatagatc agcatccaaa agcaggaacc catctaaacc
3541 agaaggaagc cctctcagat caccccagcc tcactccatt tcccacttcc acccccgtta
3601 gcttcctgca ggactctatc cctggcttcc ccttcagacc ttgcaatcac aaaaggttct
3661 tctggtgagt gcaagagcct gagactggaa aaggtggact tgtctcccag tcgaggctgg
3721 taagggacct tcagggagag ctgggcagac aggtgggaga tggaggtagg gctggctgga
3781 ggaaggaaac aacaaaggaa gtgaggtagt gccaatgaca ggacatttga catgagtctc
3841 cagatagatg tcgtggactc cagctctacg tcccacattt tagaataccc caccagcaga
3901 acaaactcag atctcatcag ggtagcagca gaggcaggac cagaaggcaa tcaagagctt
3961 ccagaaatgc cacacttgtg tgccacagag ttccccgctg acccttggtt aggggtcctc
4021 ttagtccaca aggtccggat gtcactcatg tacttaataa cacttcacct tctgtaatac
4081 taagtcctca gagctccatg ctgttctgaa agggatggcc acaagttctt tcccagcctc
4141 ttccattccc tttcttttca tgcccatccc gatgaacctg catcattccc cgacactgcc
4201 aagccaaccc tggaaaagga gttcgctggc cattggctag aatcagggtg gagaagttcc
4261 ctgaaccttc ctgtctccca gggacatgta tgcttccagg gacaagctta ggtcatgaac
4321 atggtcagaa cctttggaca agaggaaaaa tactaagaga tttgcttttt ctgggtgcgg
4381 tggctcatgc ctgtaatccc agcactttgg gaggccgagg caggtggatc atgaggtcag
4441 gagttcgagg cgagcctggc caacatggtg aaaccctgtc tctactaaaa gtacaaaaaa
4501 ttagccagtc atggtggcac acgcctgtaa tctcagctac tcaggaggct gaggcaggag
4561 aattgcttga acctgtgagg aagaggttgc agtgagctga gatcgtgcca ttacactcca
4621 gcctgggcga aagggtgaga ctccatctca aaaaaaaaaa aaatgatttg cttttgacgt
4681 cttaggtggc agggctgttc cctccaggca aatgcccttc aaaccgacga tcattgtgcc
4741 cacttaccct gggctggaga gttggtttca ggttcctaca ggagatagct ttctttccct
4801 tactccctat ctaacacttt tgctctgcag gcagccttgc ccattctcta agcctggctt
4861 agaaggcact gggaatgtcc tgtagagaga gacctagata ggtcatgcaa gtgagaaaga
4921 catctgagga aaatggaaga cctaaggcag acaggaagga agcacaaaag acaagcattg
4981 ggtcagaccc ataaaccacc tcccaaaggc tgtcatttca ttgcactgga attttgcttt
5041 atcagaagca aggaagtaag ggagtcattg ccttgggcct gggaatctaa gtgggagaca
5101 atattaattt ggatccgatt aattggagat tactaactgt ggacaaaagt ttatctttgc
5161 acaatcaata aaaatggcat ttttttagta aattaagagc ataaacaata ttgctagagg
5221 tggcatgttt agtctaccaa aaacaatact tttcaggcac tttagaaata tccttttaga
5281 agcagcgagt gcatgggcta attatcatca atctttatgt atttgttaaa gaaacatcta
5341 caggatcttt attggtgacc ttttgtaaga cattagtttg aggtactacc tatctacttg
5401 aaaataataa agtggcattt ctttatgaaa aaaaaagaaa tctcttccat aattcagatt
5461 tctacacttt atacttgcct ccctcctaaa tcgtgatatt gaaatatggt g (SEQ ID
NO:121)

FIGURE 64B

ATN2 (Na/K transport, NM_000702)

MGRGAGREYSPAATTAENGGGKKKQKEKELDELKKEVAMDDHKL

SLDELGRKYQVDLSKGLTNQRAQDVLARDGPNALTPPPTTPEWVKFCRQLFGGFSILL

WIGAILCFLAYGIQAAMEDEPSNDNLYLGVVLAAVVIVTGCFSYYQEAKSSKIMDSFK

NMVPQQALVIREGEKMQINAEEVVVGDLVEVKGGDRVPADLRIISSHGCKVDNSSLTG

ESEPQTRSPEFTHENPLETRNICFFSTNCVEGTARGIVIATGDRTVMGRIATLASGLE

VGRTPIAMEIEHFIQLITGVAVFLGVSFFVLSLILGYSWLEAVIFLIGIIVANVPEGL

LATVTVCLTLTAKRMARKNCLVKNLEAVETLGSTSTICSDKTGTLTQNRMTVAHMWFD

NQIHEADTTEDQSGATFDKRSPTWTALSRIAGLCNRAVFKAGQENISVSKRDTAGDAS

ESALLKCIELSCGSVRKMRDRNPKVAEIPFNSTNKYQLSIHEREDSPQSHVLVMKGAP

ERILDRCSTILVQGKEIPLDKEMQDAFQNAYMELGGLGERVLGFCQLNLPSGKFPRGF

KFDTDELNFPTEKLCFVGLMSMIDPPRAAVPDAVGKCRSAGIKVIMVTGDHPITAKAI

AKGVGIISEGNETVEDIAARLNIPMSQVNPREAKACVVHGSDLKDMTSEQLDEILKNH

TEIVFARTSPQQKLIIVEGCQRQGAIVAVTGDGVNDSPALKKADIGIAMGISGSDVSK

QAADMILLDDNFASIVTGVEEGRLIFDNLKKSIAYTLTSNIPEITPFLLFIIANIPLP

LGTVTILCIDLGTDMVPAISLAYEAAESDIMKRQPRNSQTDKLVNERLISMAYGQIGM

IQALGGFFTYFVILAENGFLPSRLLGIRLDWDDRTMNDLEDSYGQEWTYEQRKVVEFT

CHTAFFASIVVVQWADLIICKTRRNSVFQQGMKNKILIFGLLEETALAAFLSYCPGMG

VALRMYPLKVTWWFCAFPYSLLIFIYDEVRKLILRRYPGGWVEKETYY (SEQ ID NO:122)

FIGURE 64C

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: EMBASE BIOSIS CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0206526 (UNIV CALIFORNIA) 24 January 2002.	1-30, 37-45

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/36260

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 31-36
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claims cannot be searched because the CRF is defect.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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☐ The additional search fees were accompanied by the applicant's protest.
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